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A 34-year-old woman comes to the office due to dysuria. The patient has a history of recurrent urinary tract infections. A urine sample is collected and sent for culture. Gram-negative bacteria isolated from the urine are found to form pink colonies on lactose-containing MacConkey agar. Several days later, bacterial isolates from a second urine sample are found to form white colonies when plated on the same type of medium. Genetic analysis shows that the more recent isolates have a single nucleotide deletion within the *lac* operon DNA sequence. This genomic change is most consistent with which of the following?

- ☐ A. Conservative mutation
- ☐ B. Frameshift mutation
- ☐ C. Missense mutation
- ☐ D. Nonsense mutation
- ☐ E. Silent mutation

Submit

Block Time Remaining: 00:00:02

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A 34-year-old woman comes to the office due to **dysuria**. The patient has a history of recurrent urinary tract infections. A urine sample is collected and sent for culture. **Gram-negative** bacteria isolated from the urine are found to form pink colonies on **lactose-containing** MacConkey agar. Several days later, bacterial isolates from a second urine sample are found to form white colonies when plated on the same type of medium. Genetic analysis shows that the more recent isolates have a **single nucleotide deletion** within the *lac* operon DNA sequence. This genomic change is most consistent with which of the following?

- ☐ A. ~~Conservative mutation~~ (5%)
- ☒ B. Frameshift mutation (60%)
- ☐ C. Missense mutation (20%)
- ☐ D. Nonsense mutation (9%)
- ☐ E. ~~Silent mutation~~ (4%)

Correct

60%
Answered correctly01 min, 46 secs
Time Spent02/22/2021
Last Updated

Block Time Remaining: 00:01:46

TUTOR

<https://t.me/USMLEWorldStep1>

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Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

Exhibit Display

DNA template strand

C C C A G T G A A A C A

RNA

G G G U C A C U U U G U

Protein

Gly

Ser

Leu

Cys

Frameshift mutation

C C C A X T G A A A C A

G G G U A C U U U U G U

Gly

Tyr

Phe

In-frame deletion

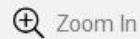
C C C X X X G A A A C A

G G G C U U U G U

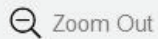
Gly

Leu

Cys



Zoom In



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Block Time Remaining: 00:01:46

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End Block



Organisms that ferment lactose appear pink on MacConkey agar whereas lactose non-fermenters form white colonies. In this case, the single nucleotide deletion within the *lac* operon DNA sequence of the newer isolates impairs lactose metabolism most likely by preventing the formation of a required enzyme. Because the mutation is a **single base deletion**, it will cause a **frameshift mutation** if it occurs within the coding region (exons) of the gene.

Frameshift mutations are caused by **deletion or insertion** of any number of nucleotides that are **not multiples of 3**. The result is a change in the reading frame during protein translation, which causes the production of an entirely different protein that is often shorter than the original due to formation of a premature stop codon.

The other mutations listed are all examples of **point mutations** (ie, single base substitutions) that can lead to a variety of changes in the coded protein.

(Choices A and C) Missense mutations are single base substitutions that result in the placement of an incorrect amino acid in a protein sequence. These mutations occur within the coding region of a gene and do not alter protein length. A conservative mutation is a type of missense mutation where an amino acid is replaced with another that has similar biochemical characteristics. Conservative mutations generally



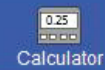
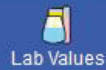
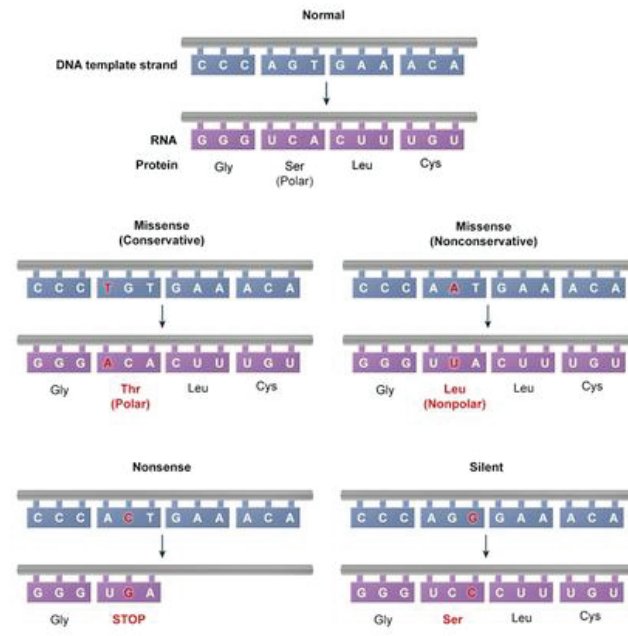
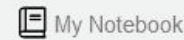
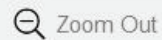
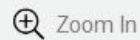


Exhibit Display

Point mutations



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Mark



Previous



Next



Full Screen



Tutorial



Lab Values



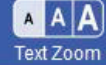
Notes



Calculator



Reverse Color



Text Zoom



Settings

(Choices A and C) Missense mutations are single base substitutions that result in the placement of an incorrect amino acid in a protein sequence. These mutations occur within the coding region of a gene and do not alter protein length. A conservative mutation is a type of missense mutation where an amino acid is replaced with another that has similar biochemical characteristics. Conservative mutations generally preserve protein function unless the mutation occurs in a critical region (eg, active site of enzyme).

(Choice D) Nonsense mutations introduce a premature stop codon in a coding region, resulting in the production of a truncated protein. The mutation described is not a nonsense mutation because it was caused by a single base **deletion** (not a base substitution).

(Choice E) A silent mutation is a single base substitution within a codon that does not change the amino acid (due to codon redundancy). Silent mutations have no effect on protein formation or function.

Educational objective:

A frameshift mutation occurs with the deletion/addition of a number of bases not divisible by 3 in the coding region of a gene. Frameshift mutations alter the reading frame of the genetic code, dramatically changing the protein structure and often resulting in the formation of a premature stop codon.

Genetics

Genetics (General Principles)

Mutations

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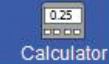
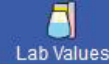
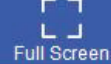
Feedback



Suspend



End Block



A 43-year-old man is evaluated for progressive neuropsychiatric symptoms. A year ago, he began feeling depressed and having hallucinations. Five months later, he developed intermittent paresthesias and progressively worsening choreiform movements, myoclonus, and ataxia. These symptoms have not improved despite multiple hospitalizations; an extensive workup has been unrevealing. The patient is a slaughterhouse worker with extensive exposure to bovine offal. As part of the evaluation for prion disease, a tissue sample digested with protease is processed via gel electrophoresis and transferred to filter paper. Antibodies to a specific prion protein are added to the filter. Next, a marked protein that combines with the antibody-protein complex is used to determine whether the test is positive. Which of the following best describes this test?

- ☐ A. Microarray
- ☐ B. Northern blot
- ☐ C. Southern blot
- ☐ D. Southwestern blot
- ☐ E. Western blot





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

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Text Zoom

Settings

depressed and having hallucinations. Five months later, he developed intermittent paresthesias and progressively worsening choreiform movements, myoclonus, and ataxia. These symptoms have not improved despite multiple hospitalizations; an extensive workup has been unrevealing. The patient is a slaughterhouse worker with extensive exposure to bovine offal. As part of the evaluation for prion disease, a tissue sample digested with protease is processed via gel electrophoresis and transferred to filter paper. Antibodies to a specific prion protein are added to the filter. Next, a marked protein that combines with the antibody-protein complex is used to determine whether the test is positive. Which of the following best describes this test?

- ☐ A. Microarray (5%)
- ☐ B. Northern blot (2%)
- ☐ C. Southern blot (3%)
- ☐ D. Southwestern blot (5%)
- ☒ E. Western blot (83%)





Western blotting is used to detect a target polypeptide or **protein** from within a mixed sample. Potential target proteins are separated by gel **electrophoresis**. The separated proteins are then transferred to a nitrocellulose membrane and probed with a primary **antibody** specific for the protein of interest. The membrane is then washed and treated with a (secondary) **marked antibody** that binds to the primary antibody and can be detected (eg, by colorimetry).

For example, a serum sample from a patient with suspected HIV infection can be analyzed via Western blot to detect antibodies directed against specific viral proteins. Following separation of viral proteins by gel electrophoresis and protein transfer to a nitrocellulose membrane, the membrane is treated with the patient's serum. Patients who are HIV positive are likely to have antibodies that react with viral p24, gp41, and gp120/160. If 2 of these 3 bands are positive, the test is considered positive.

Western blotting is similar to the enzyme-linked immunosorbent assay (ELISA) technique; however, in **ELISA** the patient's serum is tested directly, whereas in Western blotting the proteins are first separated by electrophoresis.

(Choice B) Northern blots analyze **mRNA**. A sample containing a large number of mRNA molecules is separated via gel electrophoresis. Separated bands are then transferred to a membrane and hybridized





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



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Text Zoom



Settings

(Choice B) Northern blots analyze **mRNA**. A sample containing a large number of mRNA molecules is separated via gel electrophoresis. Separated bands are then transferred to a membrane and hybridized with a probe containing a nucleotide sequence complementary to the mRNA of interest.

(Choice C) Southern blotting is used to analyze **DNA** sequences. DNA that is fragmented using restriction endonucleases is separated by gel electrophoresis and transferred to a nitrocellulose membrane. A radiolabeled DNA probe containing a sequence complementary to an area of interest is then used for hybridization. Restriction site mutations can be detected by Southern blotting because they alter DNA fragment lengths, thereby altering electrophoresis migration patterns.

Microarray analysis is similar to Southern and Northern blotting but involves hybridization of a large number of probes at once **(Choice A)**. The genomic DNA or cDNA being analyzed is labeled with a fluorescent tag and placed on a gene chip containing complementary sequences for a large number of genes. The degree of fluorescence corresponds to the mRNA expressed in the particular sample.

(Choice D) Southwestern blotting is a technique that analyzes DNA-binding proteins using principles of the Southern and Western blot techniques. DNA-binding proteins are recognized by their ability to bind specific oligonucleotide probes.

Educational objective:

Block Time Remaining: 00:03:58

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Feedback



Suspend



End Block



membrane. A radiolabeled DNA probe containing a sequence complementary to an area of interest is then used for hybridization. Restriction site mutations can be detected by Southern blotting because they alter DNA fragment lengths, thereby altering electrophoresis migration patterns.

Microarray analysis is similar to Southern and Northern blotting but involves hybridization of a large number of probes at once (**Choice A**). The genomic DNA or cDNA being analyzed is labeled with a fluorescent tag and placed on a gene chip containing complementary sequences for a large number of genes. The degree of fluorescence corresponds to the mRNA expressed in the particular sample.

(Choice D) Southwestern blotting is a technique that analyzes DNA-binding proteins using principles of the Southern and Western blot techniques. DNA-binding proteins are recognized by their ability to bind specific oligonucleotide probes.

Educational objective:

Western blotting is used to identify proteins, Northern blotting identifies specific RNA sequences, and Southern blotting identifies specific DNA sequences in an unknown sample.

Genetics

Genetics (General Principles)

Genetic testing

Subject

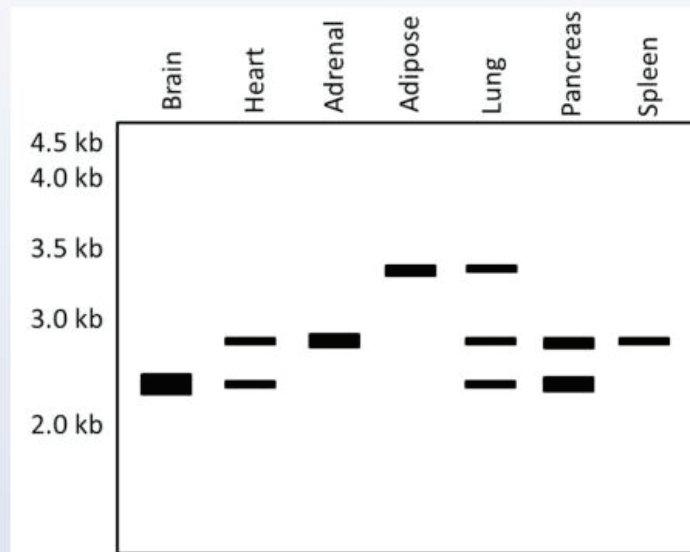
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Topic

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A researcher is studying the expression pattern of a particular gene. Messenger RNA is isolated from several tissues, subjected to electrophoresis, blotted, and probed with radiolabeled DNA containing sequences from exon 4 from that gene. An x-ray film is then placed over the blotting membrane, with the results of the autoradiogram shown below:



Which of the following best explains the autoradiogram findings in the different tissues?

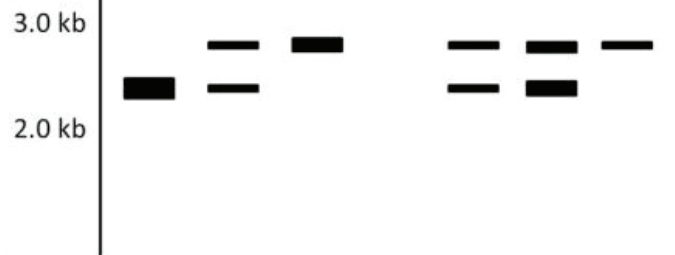


Which of the following best explains the autoradiogram findings in the different tissues?

- ☐ A. Alternate RNA splicing
- ☐ B. DNA rearrangement
- ☐ C. DNA mutation
- ☐ D. Enhancer effect
- ☐ E. Transcription factor effect

Submit





Which of the following best explains the autoradiogram findings in the different tissues?

- ☒ A. Alternate RNA splicing (78%)
- ☐ B. DNA rearrangement (4%)
- ☐ C. DNA mutation (2%)
- ☐ D. Enhancer effect (4%)
- ☐ E. Transcription factor effect (10%)

Correct

78%
Answered correctly

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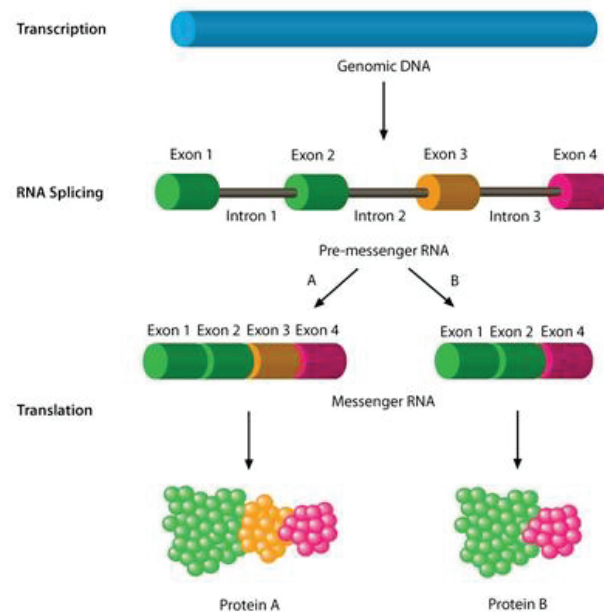
Feedback

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End Block



Exhibit Display



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Messenger RNA





The experiment described above is known as the Northern Blot technique, a procedure used to detect specific mRNA sequences in a sample to assess for gene expression. In this experiment, the Northern Blot identifies three different mRNA transcripts containing exon 4, with varying patterns of expression in the different tissues. This is consistent with alternative splicing, a process whereby the exons of the pre-mRNA produced by transcription of a gene are reconnected in multiple ways during post-transcriptional processing. The resulting finalized mRNAs are then translated into different protein isoforms. Thus, a single gene can code for multiple proteins when the same gene is spliced differently in different tissues.

Alternative splicing is a normal phenomenon in eukaryotes that greatly increases the biodiversity of proteins that can be encoded by the genome. It is thought that at least 70% of the 30,000 genes in the human genome undergo alternative splicing, and that on average, a given gene produces 4 alternatively spliced variants. Thus, the human genome is able to encode a total of 80,000 to 100,000 proteins which differ in their sequence and function.

Abnormal variations in splicing are implicated in many diseases (e.g., beta-thalassemia, cancer).

Alternative splicing also plays a prominent role in the lifecycle of many retroviruses. For instance, HIV produces a single primary RNA transcript that is alternatively spliced to produce over 40 different mRNAs.





Abnormal variations in splicing are implicated in many diseases (e.g., beta-thalassemia, cancer).

Alternative splicing also plays a prominent role in the lifecycle of many retroviruses. For instance, HIV produces a single primary RNA transcript that is alternatively spliced to produce over 40 different mRNAs.

(Choice B) DNA (gene) rearrangement occurs during the development and maturation of B cells and T cells. VDJ (**V**ariable, **D**iverse, and **J**oining) gene recombination is a random process that takes place in the primary lymphoid tissue (the bone marrow for B cells, and Thymus for T cells).

(Choice C) A mutation is a change in the DNA sequence of a gene. While somatic mutations do sporadically occur throughout the body, they do so only in a minority of cells. The vast majority of DNA throughout the body's tissues consists of identical gene coding sequences.

(Choice D & E) Transcription factors influence RNA polymerase's affinity for specific genes by binding to DNA promoter sequences or enhancer regions, which can either stimulate or inhibit gene transcription. Transcription factors and enhancer regions affect the expression of pre-mRNA, but they do not influence post-transcriptional processing.

Educational objective:

Alternative splicing is a process where the exons of a gene are reconnected in multiple ways during post-transcriptional processing. This creates different mRNA sequences and subsequently, different protein





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Educational objective:

Alternative splicing is a process where the exons of a gene are reconnected in multiple ways during post-transcriptional processing. This creates different mRNA sequences and subsequently, different protein isoforms. It is a normal phenomenon in eukaryotes that greatly increases the biodiversity of proteins encoded by the genome.

References

- [Expansion of the eukaryotic proteome by alternative splicing.](#)





An 18-year-old man comes to the urgent care clinic due to painful erythema affecting his extremities, trunk, and face. He is vacationing in Florida and spent 5 hours at a Gulf coast beach earlier in the day. The patient did not apply any sunscreen as it was cloudy. The physician explains that cloud cover does not afford a high degree of protection against the sun, especially with prolonged exposure in highly reflective environments like the beach. He is advised to wear protective clothing and apply sunscreen to prevent recurrence. Which of the following is most likely to happen within the patient's skin cells as a result of his exposure?

- ☐ A. Covalent bond formation between adjacent purine bases
- ☐ B. End-joining repair of double-stranded DNA breaks
- ☐ C. Endonuclease nicking of the damaged DNA strand
- ☐ D. Hypermethylation of residues in the undamaged DNA strand
- ☐ E. Removal of deaminated bases by glycosylase

Submit



An 18-year-old man comes to the urgent care clinic due to painful erythema affecting his extremities, trunk, and face. He is vacationing in Florida and spent 5 hours at a Gulf coast beach earlier in the day. The patient did not apply any sunscreen as it was cloudy. The physician explains that cloud cover does not afford a high degree of protection against the sun, especially with prolonged exposure in highly reflective environments like the beach. He is advised to wear protective clothing and apply sunscreen to prevent recurrence. Which of the following is most likely to happen within the patient's skin cells as a result of his exposure?

- ☒ A. Covalent bond formation between adjacent purine bases (20%)
- ☐ B. End-joining repair of double-stranded DNA breaks (13%)
- ☒ C. Endonuclease nicking of the damaged DNA strand (57%)
- ☐ D. Hypermethylation of residues in the undamaged DNA strand (3%)
- ☐ E. Removal of deaminated bases by glycosylase (5%)

Incorrect

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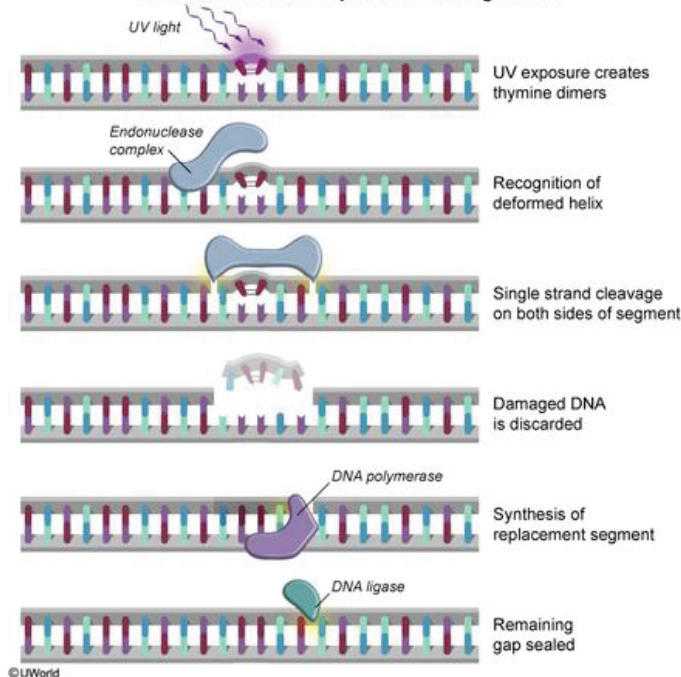


End Block



Exhibit Display

Nucleotide excision repair of UV damaged DNA



Zoom In

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Reset



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DNA can be damaged by a number of agents, including chemicals, ultraviolet radiation, and ionizing radiation. **Ultraviolet rays** damage DNA primarily through formation of abnormal covalent bonds between adjacent thymine or cytosine residues (**pyrimidine dimers**). The presence of pyrimidine dimers interferes with base recognition during transcription and replication, and **DNA mutations** can result if the damage is not repaired.

Pyrimidine dimers are removed by **nucleotide excision repair**. In this process, a specific endonuclease complex detects abnormalities in the DNA structure caused by the formation of DNA photoproducts. The endonuclease complex then **nicks** the damaged strand on both sides of the pyrimidine dimer, and the defective region is excised. DNA polymerase synthesizes new DNA in the place of the damaged DNA, and DNA ligase seals the final remaining nick.

Mutations that impair the components involved in nucleotide excision repair cause **xeroderma pigmentosum**, a condition characterized by severe photosensitivity and the development of skin cancers at a young age.

(Choice A) Ultraviolet radiation causes the formation of pyrimidine-pyrimidine dimers, not purine-purine dimers.



(Choice B) Exposure to ionizing radiation (x-rays and gamma rays) causes double-strand DNA breaks.

The fractured ends can be joined by nonhomologous end joining.

(Choice D) Incorrect base substitution occurs during normal DNA replication and can result in mutations if they are not corrected. DNA mismatch repair in certain prokaryotes is guided by hypermethylation of the parent strand, which helps to identify the non-mutated strand for use as a template.

(Choice E) Deamination of DNA bases (eg, cytosine conversion to uracil, adenine to hypoxanthine) can occur spontaneously or secondary to chemical exposure. These errors are corrected by **base excision repair**. In this process, abnormal bases are recognized and removed by specific glycosylases without disruption of the phosphodiester backbone. The apurinic and apyrimidinic residues are then removed by specific endonucleases and replaced with the correct base by DNA polymerase.

Educational objective:

Pyrimidine dimers are formed in DNA as a result of ultraviolet light exposure. They are recognized by a specific endonuclease complex that initiates the process of repair by nicking the damaged strand on both sides of the pyrimidine dimer. The damaged segment is then excised, and replacement DNA is synthesized by DNA polymerase.



In an experiment, cultured fibroblasts are mechanically lysed, and the membrane lipids and cellular proteins are chemically removed to isolate nucleic acids. The cellular extract containing the purified nucleic acids is incubated along with short sequences of repeated deoxythymidine residues fixed to latex beads. The solution is washed several times to remove unbound molecules. Which of the following types of nucleic acid is most likely to bind the strongest to the latex beads in this experiment?

- ☐ A. Aminoacyl-tRNA
- ☐ B. Mature mRNA
- ☐ C. Promoter regions of DNA
- ☐ D. Ribosomal RNA
- ☐ E. Splice sites of pre-mRNA
- ☐ F. Telomere regions of chromosomes

Submit



In an experiment, cultured fibroblasts are mechanically lysed, and the membrane lipids and cellular proteins are chemically removed to isolate nucleic acids. The cellular extract containing the purified nucleic acids is incubated along with short sequences of repeated deoxythymidine residues fixed to latex beads. The solution is washed several times to remove unbound molecules. Which of the following types of nucleic acid is most likely to bind the strongest to the latex beads in this experiment?

- ☐ A. Aminoacyl-tRNA (13%)
- ✓ ☒ B. Mature mRNA (28%)
- ☐ C. Promoter regions of DNA (28%)
- ☐ D. Ribosomal RNA (7%)
- ☐ E. Splice sites of pre-mRNA (5%)
- ☐ F. Telomere regions of chromosomes (15%)

Correct



28%

Answered correctly



01 min, 04 secs

Time Spent



03/02/2021

Last Updated

Block Time Remaining: 00:08:08

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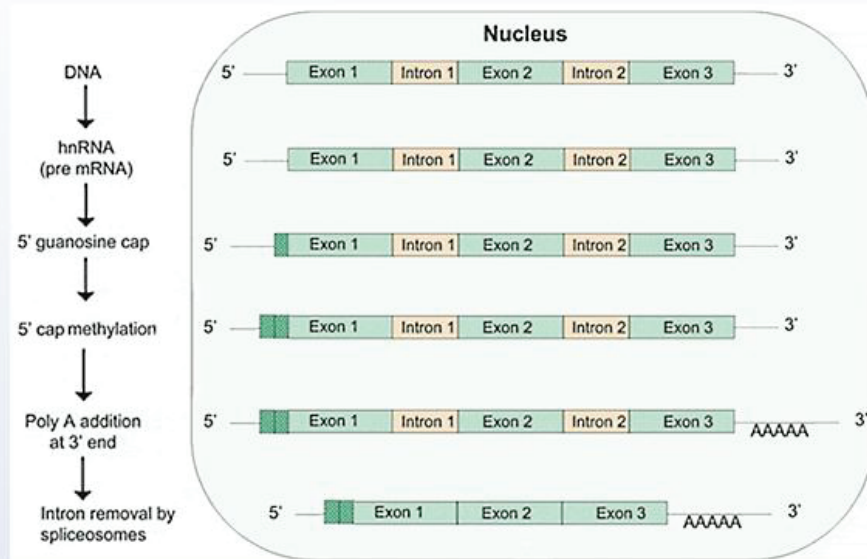
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Suspend



End Block



In the experiment described above, the poly-A tail on mature mRNA is most likely to bind the latex beads because the adenine residues in this tail would form complementary base pairs with the repeated deoxythymine residues fixed to the beads.

Mature mRNA refers to mRNA that has been processed and is ready for nuclear export and translation into protein. mRNA processing (**post-transcriptional modification**) involves the following steps:





deoxythymine residues fixed to the beads.

Mature mRNA refers to mRNA that has been processed and is ready for nuclear export and translation into protein. mRNA processing (**post-transcriptional modification**) involves the following steps:

1. 5' capping: A 7-methyl-guanosine cap is added to the 5' end of the mRNA.
2. Polyadenylation: A **poly-A tail** (chain of adenine residues) is added to most eukaryotic mRNA molecules by poly-A polymerase. Poly-A tails are not transcribed from the DNA template. Instead, a **consensus sequence (AAUAAA)** located near the 3' end of the RNA molecule directs the addition of the poly-A tail. This tail protects the mRNA from degradation within the cytoplasm after it exits the nucleus.
3. Splicing: The initial mRNA transcript (pre-mRNA) contains sequences from coding and noncoding regions of DNA, known as exons and introns, respectively. Spliceosomes (complexes of small nuclear ribonucleoproteins [snRNPs] and other proteins) remove introns containing GU at the 5' splice site and AG at the 3' splice site (**Choice E**).

(Choice A) Aminoacyl-tRNA is tRNA charged with its amino acid. The cloverleaf structure of tRNA consists of a 3' CCA tail (amino acid binding site); a T loop abundant in ribothymidine, pseudouridine, and cytidine residues; a D loop rich in dihydrouridine residues; and an anticodon loop.



(Choice A) Aminoacyl-tRNA is tRNA charged with its amino acid. The cloverleaf structure of tRNA consists of a 3' CCA tail (amino acid binding site); a T loop abundant in ribothymidine, pseudouridine, and cytidine residues; a D loop rich in dihydrouridine residues; and an anticodon loop.

(Choice C) DNA promoter regions help initiate transcription by binding transcription factors and RNA polymerase II. Promoter regions contain consensus sequences that are typically AT-rich (eg, TATA and CAAT boxes) or GC-rich (eg, GC box).

(Choice D) Ribosomal RNA (rRNA) is a component of the ribosome that catalyzes peptide bond formation during translation.

(Choice F) Telomeres are located at the ends of chromosomes and contain TTAGGG repeats, which are added by the enzyme telomerase (RNA-dependent DNA polymerase). Critical shortening in telomere length is thought to signal programmed cell death.

Educational objective:

The poly-A tail is not transcribed from DNA; instead, it is added as a post-transcriptional modification downstream of the consensus sequence (AAUAAA) located near the 3' end of the mRNA molecule. This tail protects mRNA from degradation within the cytoplasm after it exits the nucleus.

References



A 24-year-old woman comes to the office after discovering a new mole on her right leg. She is worried that it might be skin cancer as she has used tanning beds several times a year since age 18. Physical examination shows a 5-mm brown, oval macule on her anterior thigh with a homogeneous coloration and discrete borders. The lesion appears darker than her other moles. A biopsy of the lesion shows normal-appearing nevus cells clustered in the epidermis, and she is diagnosed with a benign acquired melanocytic nevus. During histologic analysis, her epithelial cells are each found to contain a condensed body composed of heavily methylated DNA at the periphery of the nucleus. This region of DNA is most likely associated with which of the following genetic findings?

- ☐ A. DNA supercoil accumulation
- ☐ B. Extensive double-strand DNA break repair
- ☐ C. Histone acetylation
- ☐ D. Impaired mismatch repair
- ☐ E. Low transcription activity





it might be **skin cancer** as she has used tanning beds several times a year since age 18. Physical examination shows a 5-mm brown, oval **macule** on her anterior thigh with a homogeneous coloration and discrete borders. The lesion appears darker than her other moles. A biopsy of the lesion shows normal-appearing nevus cells clustered in the epidermis, and she is diagnosed with a benign acquired melanocytic nevus. During histologic analysis, her epithelial cells are each found to contain a **condensed body composed of heavily methylated DNA** at the periphery of the nucleus. This region of DNA is most likely associated with which of the following genetic findings?

- ☐ A. DNA supercoil accumulation (6%)
- ☐ B. Extensive double-strand DNA break repair (7%)
- ☐ C. Histone acetylation (9%)
- ☐ D. Impaired mismatch repair (4%)
- ☒ E. Low transcription activity (71%)

Correct



71%

Answered correctly



01 min, 38 secs

Time Spent



11/21/2020

Last Updated

Block Time Remaining: 00:09:46

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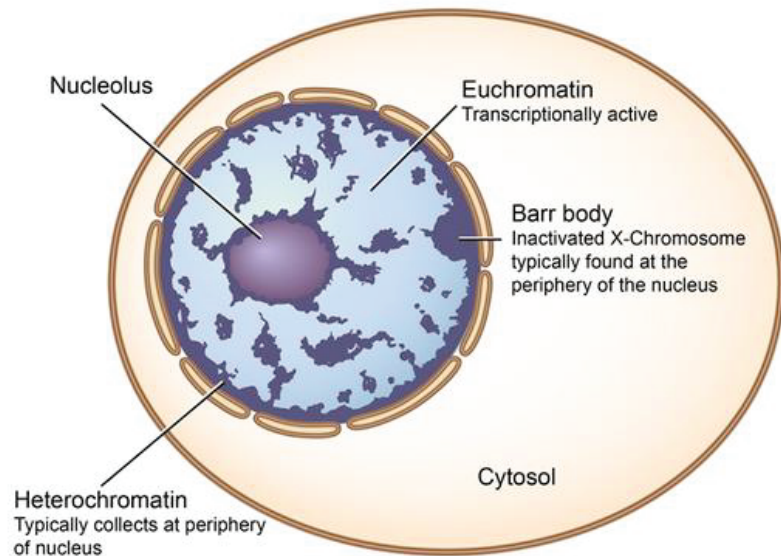


End Block



Exhibit Display

Euchromatin and heterochromatin



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Reset



New | Existing



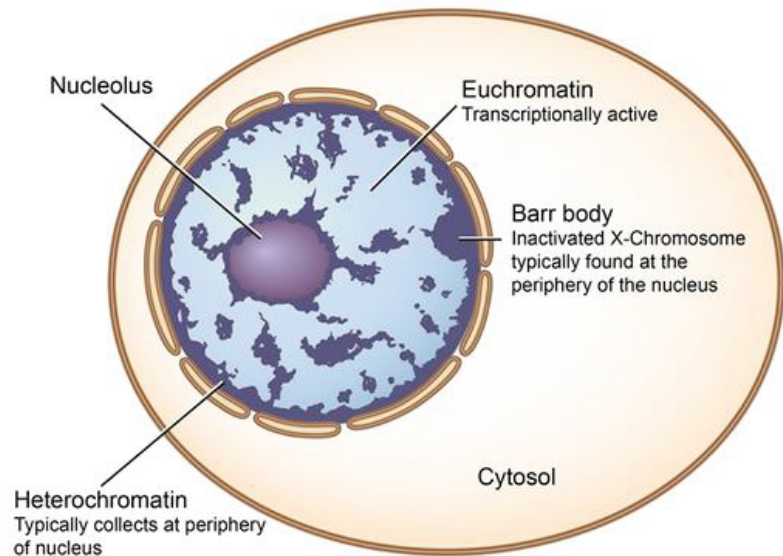
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Exhibit Display

Euchromatin and heterochromatin



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In genetically normal (46,XX) females, one X chromosome is normally randomly deactivated in each cell during early embryonic development. **X-inactivation (lyonization)** is maintained across cell division, resulting in clusters of cells throughout the body that express either the maternal or paternal X chromosome. This mosaic pattern of X-chromosome expression generally prevents X-linked recessive conditions from manifesting in female carriers. However, in rare cases, skewed lyonization (uneven inactivation of maternal/paternal X chromosome due to chance alone) may result in females developing an X-linked recessive condition (eg, classic hemophilia).

The process of lyonization converts the inactive X chromosome into condensed **heterochromatin**, which can be identified on microscopy as a compact body at the periphery of the nucleus (**Barr body**).

Heterochromatin consists of heavily **methyated DNA** (eg, cytosine converted to methylcytosine) and **deacetylated histones**, which cause it to have a low level of transcriptional activity (**Choice C**). A small proportion of genes remain transcriptionally active on the inactivated X chromosome. For this reason, inheritance of an abnormal number of X chromosomes can cause clinical manifestations due to a gene-dosage effect, as seen with Turner (45,XO) and Klinefelter (47,XXY) syndromes.

(Choice A) During DNA replication, positive supercoiling occurs in the region ahead of the replication fork and must be removed for DNA replication to proceed. Topoisomerase reduces DNA supercoiling by





dosage effect, as seen with Turner (45,XO) and Klinefelter (47,XXY) syndromes.

(Choice A) During DNA replication, positive supercoiling occurs in the region ahead of the replication fork and must be removed for DNA replication to proceed. Topoisomerases reduce DNA supercoiling by nicking the DNA strands, introducing negative coiling, and religating the strands.

(Choice B) Double-strand DNA breakage can occur following exposure to ionizing radiation. Compared to single-strand breakage, double-stranded breaks are more prone to result in faulty repair, leading to mutations, malignancy, or cell death.

(Choice D) Repair of mismatched bases occurs throughout the genome during DNA replication. Impaired mismatch repair is associated with hereditary nonpolyposis colorectal cancer.

Educational objective:

X-inactivation occurs in genetically normal females and results in conversion of the inactivated X chromosome into compact heterochromatin (Barr body). Heterochromatin is condensed chromatin composed of heavily methylated DNA in tight association with deacetylated histones. It has a low level of transcriptional activity. In contrast, euchromatin is loosely arranged and exhibits a high level of transcriptional activity.





Molecular biologists undertake a series of experiments designed to classify proteins involved in various intracellular signaling pathways. During one of the experiments, a protein mixture obtained from a cell culture is separated by gel electrophoresis and subsequently transferred to a filter membrane. Labeled double-stranded DNA probes are then used to detect a specific protein of interest in the sample. Which of the following proteins is most likely to be detected by this method?

- ☐ A. Ras
- ☐ B. c-Jun
- ☐ C. β 1-adrenoreceptor
- ☐ D. S-100
- ☐ E. Adenylate cyclase

Submit



Molecular biologists undertake a series of experiments designed to classify proteins involved in various intracellular signaling pathways. During one of the experiments, a protein mixture obtained from a cell culture is separated by gel electrophoresis and subsequently transferred to a filter membrane. Labeled double-stranded DNA probes are then used to detect a specific protein of interest in the sample. Which of the following proteins is most likely to be detected by this method?

- ☐ A. Ras (35%)
- ✓ ☒ B. c-Jun (27%)
- ☐ C. β 1-adrenoreceptor (3%)
- ☐ D. S-100 (13%)
- ☐ E. Adenylate cyclase (19%)

Correct

27%
Answered correctly01 min, 51 secs
Time Spent02/28/2021
Last Updated



Blotting technique	Substance detected	Type of probe
Northern	RNA	Single-stranded DNA or RNA (hybridization probe)
Southern	DNA	
Western	Protein	Antibody
Southwestern	DNA-binding protein	Double-stranded DNA

The Southern, Western, Northern, and Southwestern blot procedures are powerful techniques used to analyze and identify DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The same basic technique underlies all of the blot procedures. First, the unknown sample is separated by gel electrophoresis. Separation occurs based on a molecule's size and charge. The separated molecules form bands on the gel that are then blotted onto a nitrocellulose membrane and incubated with a labeled





The Southern, Western, Northern, and Southwestern blot procedures are powerful techniques used to analyze and identify DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The same basic technique underlies all of the blot procedures. First, the unknown sample is separated by gel electrophoresis. Separation occurs based on a molecule's size and charge. The separated molecules form bands on the gel that are then blotted onto a nitrocellulose membrane and incubated with a labeled probe to identify the specific DNA fragment, RNA molecule, or protein of interest.

Southwestern blots are used to identify and isolate proteins that bind DNA. In this technique, the target protein binds to a labeled, double-stranded DNA probe that is homologous to the protein's regulatory sequence. Of the molecules listed, c-Jun is the only DNA-binding protein. c-Jun and c-Fos are nuclear transcription factors that directly bind DNA via a leucine zipper motif. The genes that code for c-Jun and c-Fos are proto-oncogenes, genes that can become oncogenes following a mutation or with constitutive expression.

(Choice A) Ras is a proto-oncogene that codes for a membrane-bound G-protein. This G-protein acts as a secondary mediator for several hormones and cytokines that act on cell membrane receptors. Ras activation activates the MAP kinase pathway and ultimately affects transcription. However, Ras itself does not bind directly to DNA.





(Choices C and E) The β_1 -adrenergic receptor is a classic G_s -protein-coupled receptor located in the cell membrane. It does not interact directly with DNA. Adenylyl cyclase is the enzyme that cleaves ATP to form cAMP, the second messenger associated with G_s -protein-coupled receptors. cAMP activates protein kinase A for further downstream signaling.

(Choice D) S-100 proteins are homodimeric calcium-binding proteins, similar in structure to calmodulin and important in intracellular functions such as protein phosphorylation and cell growth and differentiation. S-100 is a marker for cells of neural crest derivation (melanocytes and Schwann cells), as well as Langerhans cells and other dendritic cells.

Educational objective:

Southwestern blotting is used to detect DNA-binding proteins such as transcription factors, nucleases, and histones.

References

- [Southwestern blotting in investigating transcriptional regulation.](#)

Biochemistry

Genetics (General Principles)

Dna structure & function

Subject

System

Topic





A 32-year-old man is recovering from extensive burns. Fibroblasts near the site of injury actively synthesize precursor mRNA to be used as templates for protein synthesis. After transcription, extensive processing of the precursor RNA occurs to form the finalized mRNA sequence. The finalized mRNA then exits the nucleus and undergoes translation by ribosome complexes before being degraded. Which of the following steps involving the processing and handling of mRNA occurs only within the cytoplasm of cells?

- ☐ A. 5'-terminal guanosine triphosphate addition
- ☐ B. Methylation of the 5'-terminal guanine
- ☐ C. Multiple adenine nucleotide attachment to the 3'-end
- ☐ D. Interaction with snRNP
- ☐ E. Removal of intervening sequences
- ☐ F. Interaction with P bodies

Submit



A 32-year-old man is recovering from extensive burns. Fibroblasts near the site of injury actively synthesize precursor mRNA to be used as templates for protein synthesis. After transcription, extensive processing of the precursor RNA occurs to form the finalized mRNA sequence. The finalized mRNA then exits the nucleus and undergoes translation by ribosome complexes before being degraded. Which of the following steps involving the processing and handling of mRNA occurs only within the cytoplasm of cells?

- ☐ A. ~~5'-terminal guanosine triphosphate addition~~ (6%)
- ☐ B. ~~Methylation of the 5'-terminal guanine~~ (13%)
- ☐ C. ~~Multiple adenine nucleotide attachment to the 3'-end~~ (11%)
- ☐ D. ~~Interaction with snRNP~~ (14%)
- ☐ E. ~~Removal of intervening sequences~~ (8%)
- ☒ F. Interaction with P bodies (44%)

Correct



44%

Answered correctly



01 min, 02 secs

Time Spent



01/29/2021

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Block Time Remaining: 00:12:39

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After transcription, the preliminary, unprocessed mRNA is known as precursor mRNA, or heterogeneous nuclear RNA (hnRNA). Eukaryotic pre-mRNA undergoes significant posttranscriptional processing before leaving the nucleus, including 5'-capping, poly A tail addition, and intron splicing.

Once mRNA is finalized, it leaves the nucleus bound to specific packaging proteins. Upon entering the cytoplasm, these mRNA complexes often associate with ribosomes to undergo translation. However, certain mRNA sequences instead associate with proteins that are found in P bodies. P bodies are distinct foci found within eukaryotic cells that are involved in mRNA regulation and turnover. They play a fundamental role in translation repression and mRNA decay, and contain numerous proteins including RNA exonucleases, mRNA decapping enzymes, and constituents involved in mRNA quality control and microRNA-induced mRNA silencing. P bodies also seem to function as a form of mRNA storage, as certain mRNAs are incorporated into P bodies only to be later released and utilized for protein translation.

(Choices A and B) The 5' end of all mRNA is capped with a 7-methylguanosine residue by a unique 5' to 5' linkage, which occurs in two stages. The first step is the addition of guanine triphosphate to the 5' end of mRNA in a reaction catalyzed by guanylyltransferase. Methylation of the guanosine cap is then catalyzed by guanine-7-methyltransferase. Capping of the precursor RNA occurs in the nucleus as the RNA is being transcribed. This methylated cap protects mRNA from degradation by cellular exonucleases, and allows it



transcribed. This methylated cap protects mRNA from degradation by cellular exonucleases, and allows it to exit the nucleus.

(Choice C) mRNA is polyadenylated at the 3' end by the polyadenylate polymerase complex, which recognizes a specific sequence (AAUAAA), cleaves the pre-mRNA molecule a few residues downstream from this sequence, and then adds a stretch of 20 - 250 adenine residues called the poly A tail. The addition of the poly A tail occurs before the mRNA exits the nucleus. In the cytosol, the poly A tail is gradually shortened, eventually leading to mRNA degradation.

(Choices D and E) Since pre-mRNA contains both introns and exons, and only exons code for proteins, introns must be excised before translation through a process known as splicing. Splicing of pre-mRNA occurs within the nucleus and is facilitated by the interaction of pre-mRNA with small ribonucleoprotein particles called snRNPs (or "snurps" for short).

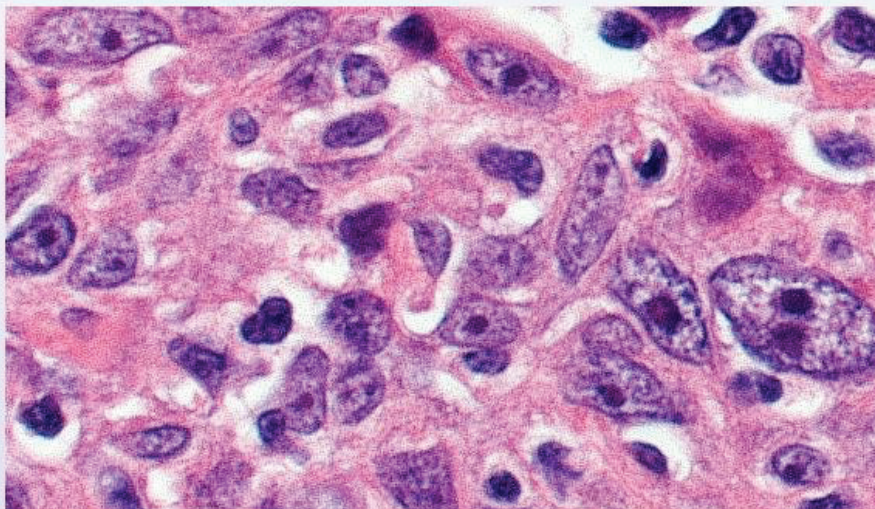
Educational objective:

When mRNA is first transcribed from DNA, it is in an unprocessed form called pre-mRNA or heterogeneous nuclear mRNA (hnRNA). Several processing steps are required before finalized mRNA molecules can leave the nucleus, including 5'-capping, poly A tail addition, and intron splicing. Cytoplasmic P bodies play an important role in mRNA translation regulation and mRNA degradation.

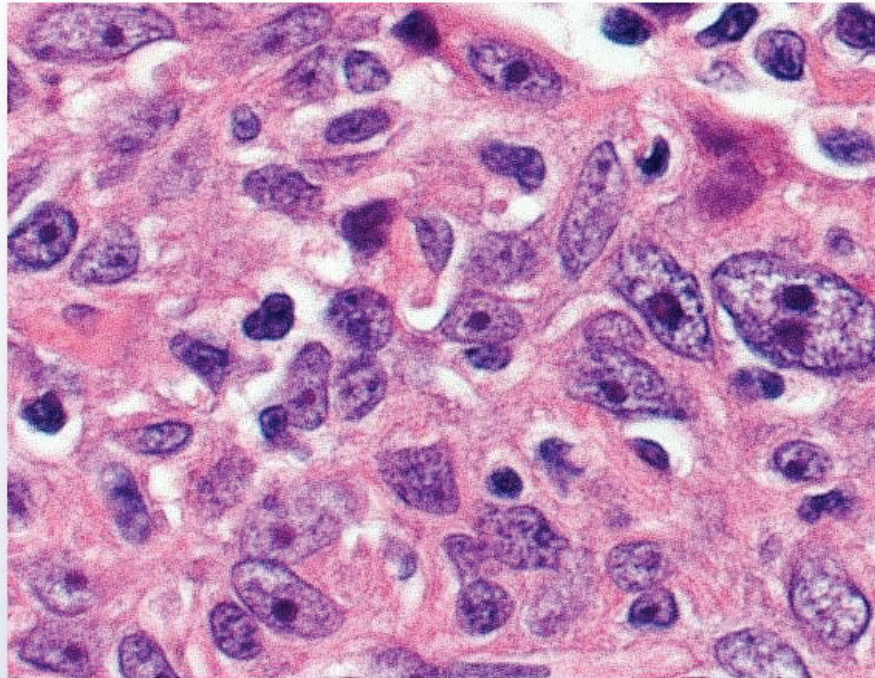
References



A 58-year-old man comes to the office with a persistent dry cough. He has experienced an involuntary weight loss of 10 kg (22 lb) over the last 3 months. The patient drinks 2-3 beers daily and has a 40-pack-year smoking history. Physical examination shows dullness to percussion over the right lower lung base. A chest CT reveals a right-sided pleural effusion and a mass in the lower lobe of the right lung. Transbronchial biopsy of the mass demonstrates malignant cells with large nuclei that contain prominent, round, basophilic bodies as shown below.

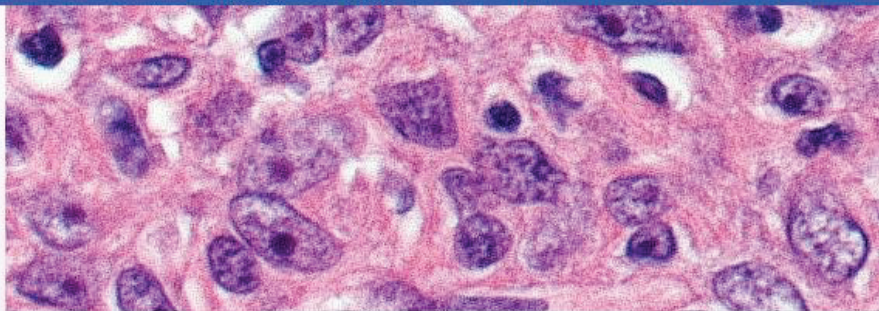


round, basophilic bodies as shown below.



Which of the following enzymes is most likely to function only within this basophilic region of the nucleus?

☐ A. DNA endonuclease

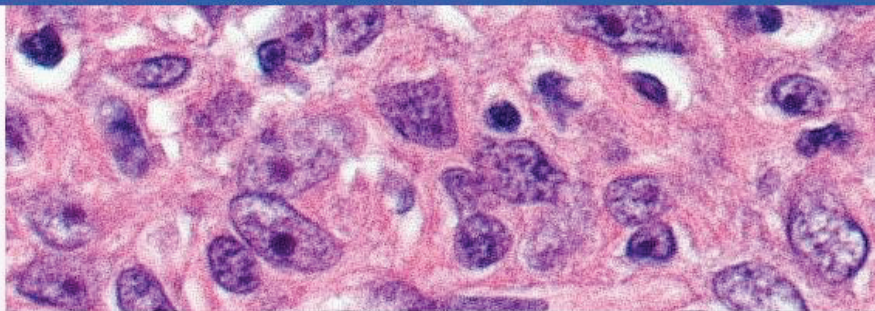


Which of the following enzymes is most likely to function only within this basophilic region of the nucleus?

- ☐ A. DNA endonuclease
- ☐ B. DNA polymerase
- ☐ C. RNA polymerase I
- ☐ D. RNA polymerase II
- ☐ E. RNA polymerase III

Submit





Which of the following enzymes is most likely to function only within this **basophilic region** of the nucleus?

- ☐ A. DNA endonuclease (11%)
- ☐ B. DNA polymerase (27%)
- ☒ C. RNA polymerase I (34%)
- ☐ D. RNA polymerase II (18%)
- ☐ E. RNA polymerase III (7%)





Exhibit Display

Synthesis & function of eukaryotic RNA		
Synthesizing polymerase	Type of RNA produced	Function
RNA polymerase I	18S, 5.8S & 28S ribosomal RNA	Form essential ribosomal components
RNA polymerase II	Messenger RNA	Translated by ribosomes to form specific proteins
	Small nuclear RNA	Involved in mRNA splicing & transcription regulation
	Micro RNA	Cause gene silencing via translation arrest or mRNA degradation
RNA polymerase III	Transfer RNA	Adaptor molecule linking codons with specific amino acids
	5S ribosomal RNA	Essential component of 60S ribosomal subunit

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The **nucleolus** is a round, dense, basophilic (dark-staining) body that can be identified within the nucleus on standard light microscopy. It is the primary site of ribosomal RNA (rRNA) transcription. Although there are several hundred copies of the 45S pre-rRNA gene divided among multiple chromosomes, these are arranged into clusters called nucleolar organizing regions that position themselves so that all copies are located within the nucleolus. **RNA polymerase I** functions exclusively to transcribe the **45S pre-rRNA** gene into a single template that is subsequently processed into mature **18S**, **5.8S**, and **28S rRNAs**. As such, the function of RNA polymerase I is restricted to the nucleolus.

In addition to transcribing rRNA, the nucleolus is also involved in the maturation and assembly of ribosomal subunits. Ribosomal protein components are synthesized in the cytoplasm and transported into the nucleolus, where they combine with rRNA to form immature 40S and 60S subunits that are then shuttled out of the nucleus via nuclear pores. Regulation of ribosomal synthesis occurs in part by controlling the number of active rRNA genes. Generally, as cells become more differentiated, their growth slows and they require fewer numbers of ribosomes for protein production. In contrast, **malignant cells** with high metabolic activity usually have a large number of active rRNA genes and **prominent nucleoli**.

(Choice A) Endonucleases break the phosphodiester bond within the nucleotide chain in DNA and RNA. They are important in DNA repair and RNA splicing and are present throughout the nucleoplasm.





Item 9 of 40

Question Id: 2039



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom

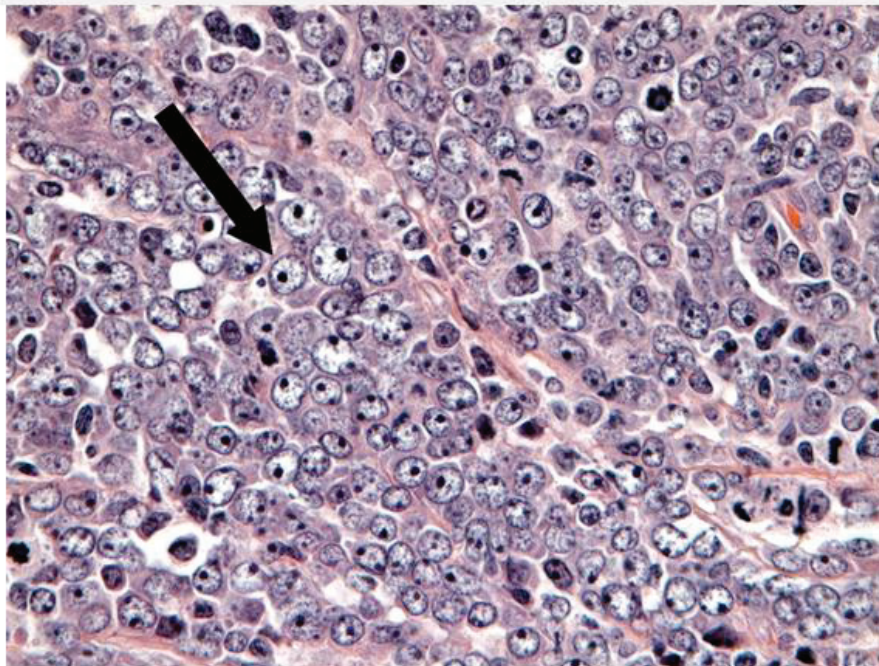


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Exhibit Display

Diffuse large B-cell lymphoma Lymphoepithelial carcinoma



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They are important in DNA repair and RNA splicing and are present throughout the nucleoplasm.

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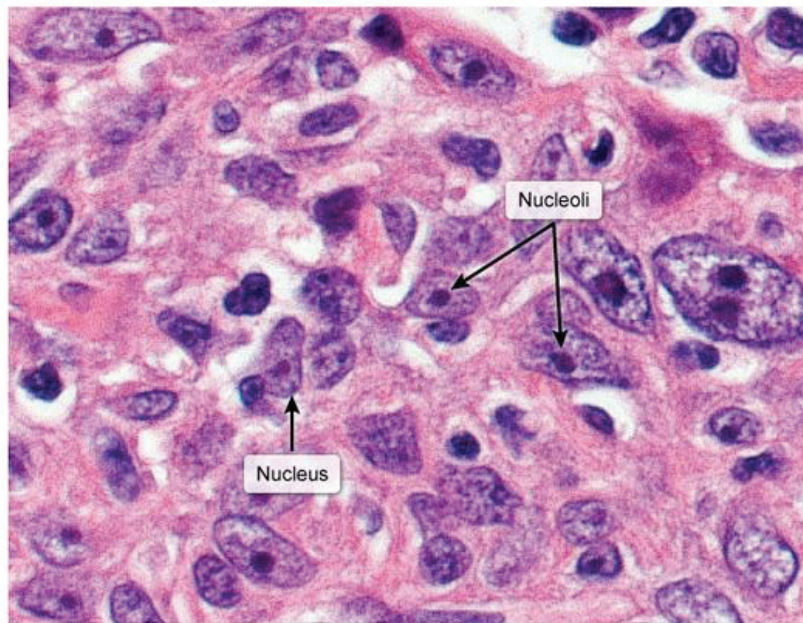


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Exhibit Display

Diffuse large B-cell lymphoma [Lymphoepithelial carcinoma](#)

Carcinoma



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metabolic activity usually have a large number of active rRNA genes and prominent nucleoli.

(Choice A) Endonucleases break the phosphodiester bond within the nucleotide chain in DNA and RNA.

They are important in DNA repair and RNA splicing and are present throughout the nucleoplasm.

(Choice B) DNA polymerases are the primary enzymes responsible for DNA replication and repair. They are found throughout the nucleus.

(Choice D) RNA polymerase II synthesizes messenger RNA (mRNA), small nuclear RNA (snRNA), and micro RNA (miRNA). It is the most highly regulated of the 3 RNA polymerases, with its function determined by multiple transcription factors and regulatory processes.

(Choice E) RNA polymerase III transcribes DNA to form small RNA molecules such as transfer RNA (tRNA) and 5S rRNA. Unlike other rRNA molecules, the genes for the 5S rRNA are located outside the nucleolus.

Educational objective:

The nucleolus is the site of ribosomal subunit maturation and assembly. RNA polymerase I functions exclusively within the nucleolus to transcribe the 45S pre-rRNA gene, which codes for most of the ribosomal RNA components (18S, 5.8S, and 28S rRNAs).

References



In an experiment, erythrocyte precursor cells are incubated in a medium containing radiolabeled cysteine. These radiolabeled cysteine residues are attached to their appropriate tRNAs by the enzyme aminoacyl-tRNA synthetase. The bound cysteine residues are then chemically modified to form alanine. The end product of this reaction is a tRNA molecule that contains the cysteine anticodon but is mischarged with alanine. Which of the following is most likely to occur to this alanine residue during polypeptide synthesis of alpha-hemoglobin?

- ☐ A. It will be incorporated into the polypeptide chain at a site requiring alanine
- ☐ B. It will be incorporated into the polypeptide chain at a site requiring cysteine
- ☐ C. It will be randomly incorporated into the polypeptide chain, halting chain elongation
- ☐ D. It will be rapidly cleaved off tRNA by the enzyme glycosylase
- ☐ E. It will never be incorporated into the polypeptide chain and will remain attached to tRNA

Submit



In an experiment, erythrocyte precursor cells are incubated in a medium containing radiolabeled cysteine. These radiolabeled cysteine residues are attached to their appropriate tRNAs by the enzyme aminoacyl-tRNA synthetase. The bound cysteine residues are then chemically modified to form alanine. The end product of this reaction is a tRNA molecule that contains the cysteine anticodon but is mischarged with alanine. Which of the following is most likely to occur to this alanine residue during polypeptide synthesis of alpha-hemoglobin?

- ☐ A. It will be incorporated into the polypeptide chain at a site requiring alanine (5%)
- ☒ B. It will be incorporated into the polypeptide chain at a site requiring cysteine (69%)
- ☐ C. It will be randomly incorporated into the polypeptide chain, halting chain elongation (5%)
- ☐ D. It will be rapidly cleaved off tRNA by the enzyme glycosylase (13%)
- ☐ E. It will never be incorporated into the polypeptide chain and will remain attached to tRNA (6%)

Correct



69%

Answered correctly



01 min, 14 secs

Time Spent



03/07/2021

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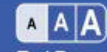


Amino acid activation and attachment to the 3' end of tRNA are catalyzed by **aminoacyl-tRNA synthetases** (AA-tRNA synthetases). Each amino acid/tRNA pair has a specific AA-tRNA synthetase that links them together. These enzymes are responsible for ensuring that each amino acid binds to the tRNA with the proper anticodon. AA-tRNA synthetase activation and binding sites are **highly specific** for their correct amino acids and tRNA molecules. In addition, some AA-tRNA synthetases can "**proofread**" their specific tRNA molecules and hydrolyze the amino acid bond when their tRNAs are incorrectly charged. The error rate for AA-tRNA synthetases is therefore very low, with less than 1 error per 10^4 charges.

During protein synthesis, tRNA acts as an adaptor molecule between the codons found on mRNA and the amino acids being incorporated into the polypeptide chain. The amino acid sequence in a polypeptide chain is dictated by the binding of a tRNA anticodon to its complementary codon on the mRNA molecule being translated. **Erroneous amino acid/tRNA coupling** by AA-tRNA synthetase causes the **wrong amino acid** to be **incorporated** into the growing polypeptide chain (**Choice E**).

For example, under normal circumstances, when the ribosome encounters a cysteine codon (eg, UGU) on mRNA, the complementary tRNA anticodon (eg, ACA) binds. If this tRNA is improperly charged with alanine, as described in the experiment above, alanine will be incorrectly incorporated into the growing polypeptide chain in place of cysteine (**Choice A**).





alanine, as described in the experiment above, alanine will be incorrectly incorporated into the growing polypeptide chain in place of cysteine **(Choice A)**.

(Choice C) During polypeptide chain elongation, ribosomes move from codon to codon on mRNA in the 5' to 3' direction, sequentially adding amino acids from aminoacyl-tRNA to the peptide chain. This continues until the ribosome encounters a stop codon (ie, UAA, UAG, or UGA). Releasing factors then assist in polypeptide chain termination.

(Choice D) DNA glycosylases are enzymes involved in DNA base excision repair.

Educational objective:

The sequence of amino acids in a growing polypeptide chain is dictated by the interaction of the mRNA codon with the tRNA anticodon. tRNA that is mischarged with the incorrect amino acid (and not corrected by aminoacyl-tRNA synthetase proofreading) will incorporate the wrong amino acid into the growing polypeptide chain.

References

- [Quality control in aminoacyl-tRNA synthesis its role in translational fidelity.](#)

Genetics

Genetics (General Principles)

Rna structure & function

Block Time Remaining: 00:15:49

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A 5-year-old girl is brought to the office by her mother because she is concerned that her daughter "sunburns too easily." The mother says the patient's skin becomes red and scaly with only minimal sun exposure. She first noticed the problem when her daughter was 7 months old during a trip to the beach. The mother has since avoided exposing her child to excess sunlight, but finds it difficult now that the patient has begun kindergarten. Physical examination shows thin and hyperpigmented skin. She also has a few nevi on her hands that have been enlarging rapidly. This patient's disorder is most likely due to a primary defect involving which of the following processes?

- ☐ A. DNA mismatch repair
- ☐ B. Nucleotide excision repair
- ☐ C. Ras signal transduction
- ☐ D. Regulation of apoptosis
- ☐ E. Regulation of cell cycle
- ☐ F. Repair of DNA crosslinks





"sunburns" too easily." The mother says the patient's skin becomes red and scaly with only minimal sun exposure. She first noticed the problem when her daughter was 7 months old during a trip to the beach. The mother has since avoided exposing her child to excess sunlight, but finds it difficult now that the patient has begun kindergarten. Physical examination shows thin and hyperpigmented skin. She also has a few nevi on her hands that have been enlarging rapidly. This patient's disorder is most likely due to a primary defect involving which of the following processes?

- ☐ A. DNA mismatch repair (10%)
- ☒ B. Nucleotide excision repair (71%)
- ☐ C. Ras signal transduction (1%)
- ☐ D. Regulation of apoptosis (1%)
- ☐ E. Regulation of cell cycle (1%)
- ☐ F. Repair of DNA crosslinks (13%)

Correct

71%



52 secs



02/22/2021

Block Time Remaining: 00:16:41

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This patient likely has **xeroderma pigmentosum**, a rare autosomal recessive disorder that occurs due to defective **nucleotide excision repair** of DNA damaged by **ultraviolet (UV) light**. Normally, the regions of DNA damaged by UV radiation are excised and replaced by a series of DNA repair enzymes. In xeroderma pigmentosum, this process is impaired and leads to the accumulation of abnormal pyrimidine nucleotides and other carcinogenic adducts.

The skin of affected individuals is normal at birth, but they present during the first year of life with severe sun sensitivity (eg, erythema, scaling) affecting light-exposed areas, especially the face. Later, the skin shows atrophy, telangiectasias, and intermingling areas of hypo- and hyperpigmentation due to chronic UV damage. **Skin malignancies**, including malignant melanoma and squamous and basal cell carcinoma, develop as early as ages 5-6.

(Choice A) Abnormalities of genes responsible for DNA mismatch repair are found in patients with hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome). These patients have a greater incidence of colorectal, endometrial, and ovarian cancer.

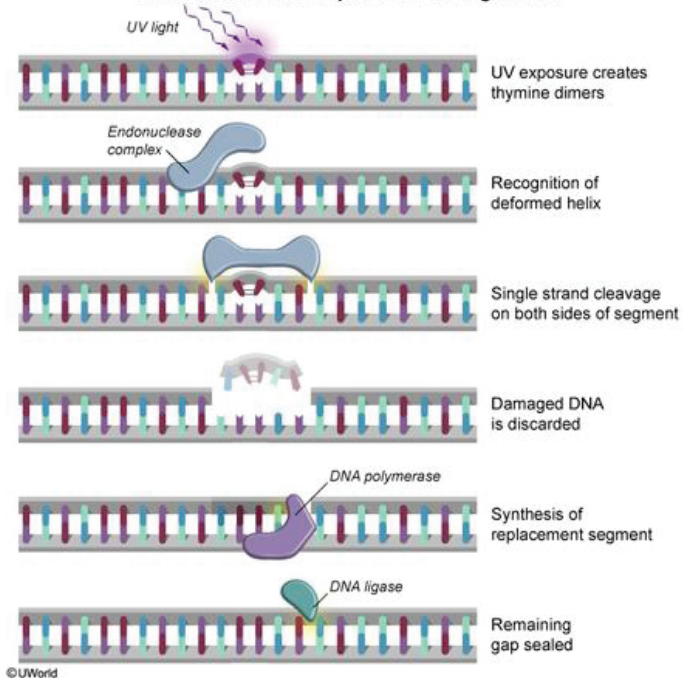
(Choice C) Ras codes for a G protein that regulates growth factor signal transduction. Mutations that result in a constitutively activated Ras protein cause constant and unregulated cell proliferation, leading to malignancy (particularly pancreatic and colorectal cancer).





Exhibit Display

Nucleotide excision repair of UV damaged DNA



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(Choice C) Ras codes for a G protein that regulates growth factor signal transduction. Mutations that result in a constitutively activated Ras protein cause constant and unregulated cell proliferation, leading to malignancy (particularly pancreatic and colorectal cancer).

(Choices D and E) p53 is a regulatory protein that halts cell cycle progression when DNA is damaged, allowing time for the DNA to be repaired. When the damage is irreversible, apoptosis is triggered. Acquired p53 mutations are found in the majority of spontaneous cancers, whereas inherited p53 mutations are responsible for Li-Fraumeni syndrome (which causes a wide range of malignancies at a young age).

(Choice F) Fanconi anemia is an autosomal recessive condition caused by mutations in the genes responsible for the repair of interstrand DNA crosslinks. It is the most common inherited cause of aplastic anemia and presents with short stature, absent thumbs, and increased malignancy risk.

Educational objective:

Xeroderma pigmentosum develops due to a defect in nucleotide excision repair. This disease is characterized by increased sensitivity to ultraviolet radiation and a high incidence of cutaneous malignancy.

References

- [Xeroderma pigmentosum](#)
- [Deep phenotyping of 89 xeroderma pigmentosum patients reveals unexpected heterogeneity](#)





A married couple comes to the physician for routine prenatal counseling. The husband is 120 cm (3 ft 11 in) tall with disproportionately short upper and lower extremities, a large head, and a prominent forehead. He is unable to provide a biological family history as he was adopted. His spouse is of average height with normal constitutional features, and her family history is insignificant. They are concerned about their unborn child's height. Which of the following is the best response to their concerns?

- ☐ A. The condition is not inheritable
- ☐ B. The risk depends on the child's biological sex
- ☐ C. The risk depends on the mother's carrier status
- ☐ D. The risk for the child to be short is about 25%
- ☐ E. The risk for the child to be short is about 50%

Submit



A married couple comes to the physician for routine prenatal counseling. The husband is 120 cm (3 ft 11 in) tall with disproportionately short upper and lower extremities, a large head, and a prominent forehead. He is unable to provide a biological family history as he was adopted. His spouse is of average height with normal constitutional features, and her family history is insignificant. They are concerned about their unborn child's height. Which of the following is the best response to their concerns?

- ☐ A. ~~The condition is not inheritable~~ (7%)
- ☐ B. The risk depends on the child's biological sex (3%)
- ☐ C. The risk depends on the mother's carrier status (13%)
- ☐ D. The risk for the child to be short is about 25% (7%)
- ✓ ☒ E. The risk for the child to be short is about 50% (68%)

Correct



68%

Answered correctly



54 secs

Time Spent



10/10/2020

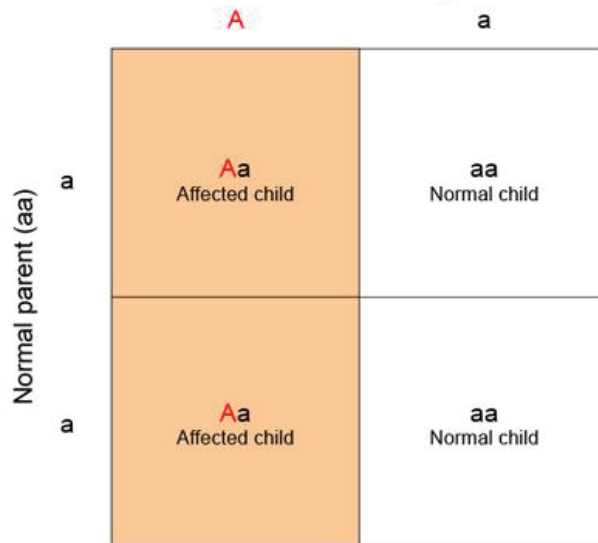
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Exhibit Display

Autosomal dominant inheritance

Affected parent (Aa)

Offspring have 50% chance of being affected

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The husband's short stature and morphologic features are suggestive of **achondroplasia**. Achondroplasia is the most common form of short-limbed dwarfism and is caused by a mutation that results in constitutive activation of **fibroblast growth factor receptor 3 (FGFR3)**.

Achondroplasia occurs as a sporadic mutation (due to advanced paternal age) in 85% of cases. However, once a mutation occurs, it can be transmitted as an **autosomal dominant** trait (responsible for the remaining 15% of cases) (**Choice A**). Only **1 mutant copy** of the FGFR3 gene is sufficient to cause the disorder; **2 copies** of the mutant gene (ie, homozygosity) are **lethal**. As a result, the husband must be heterozygous for the achondroplasia mutation.

A **heterozygous parent** has a **50% chance** of transmitting an autosomal dominant mutation. Therefore, the unborn child has a 50% chance of inheriting achondroplasia. Because achondroplasia is a rare condition, the chance of the unborn child having a sporadic (de novo) mutation does not significantly add to the 50% risk of inheriting the disease.

(Choice B) In sex-linked disorders, the responsible gene is located on a sex chromosome (either X or Y). Most sex-linked disorders are X-linked recessive (XLR). In **XLR disorders**, women with a copy of the defective gene will not have the disorder but will be carriers; men who inherit the defective gene will be

(Choice B) In sex-linked disorders, the responsible gene is located on a sex chromosome (either X or Y).

Most sex-linked disorders are X-linked recessive (XLR). In **XLR disorders**, women with a copy of the defective gene will not have the disorder but will be carriers; men who inherit the defective gene will be affected. In **X-linked dominant disorders**, both males and females are affected following inheritance of the defective gene.

(Choice C) Inheritance of an AD trait does not always result in the disease phenotype in conditions with incomplete penetrance. However, achondroplasia is a fully penetrant genetic disorder; if the mother carried the trait, she would have short stature.

(Choice D) About 25% of children are affected in **autosomal recessive (AR)** disorders if both parents carry 1 copy of the defective gene (most common scenario). Many AR disorders are the result of enzymatic deficiencies (eg, phenylketonuria) that require both copies of the gene to be knocked out, as 1 functional copy usually provides sufficient activity to prevent occurrence of the disease.

Educational objective:

Achondroplasia is an autosomal dominant (AD) disorder that results in a gain-of-function mutation in the FGFR3 gene. Most individuals affected by AD disorders are heterozygous and have a 50% chance of transmitting the mutation to their offspring.



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

(Choice B) In sex-linked disorders, the responsible gene is located on a sex chromosome (either X or Y).

Exhibit Display

X-linked recessive inheritance

Affected father

		Mother			
		X	X		
Father	X ^d	XX ^d	XX ^d	All daughters are carriers	
	Y	XY	XY	All sons are normal	

Carrier mother

		Mother			
		X	X ^d		
Father	X	XX	XX ^d	Daughters have 50% chance of becoming carriers	
	Y	XY	X ^d Y	Sons have 50% chance of being affected	

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Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

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(Choice B) In sex-linked disorders, the responsible gene is located on a sex chromosome (either X or Y).

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X-linked dominant inheritance

Affected father

		Mother			
		X		X	
Father	X ^d	XX ^d		XX ^d	All daughters are affected
	Y	XY		XY	All sons are normal

Affected mother

		Mother			
		X		X ^d	
Father	X	XX		XX ^d	All sons & daughters have 50% chance of being affected
	Y	XY		X ^d Y	

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Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

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(Choice B) In sex-linked disorders, the responsible gene is located on a sex chromosome (either X or Y).

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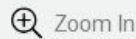
Autosomal recessive inheritance

Carrier parent (Aa)

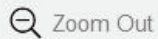
	A	a
A	AA Normal child	Aa Carrier child
a	Aa Carrier child	aa Affected child

Offspring have 25% chance of being affected

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A pharmaceutical researcher develops a novel antibacterial drug that works by inhibiting exonuclease activity during DNA replication. When actively dividing *Escherichia coli* is exposed to the drug, enzyme-mediated nucleotide removal in the 5' to 3' direction is impaired, leading to inhibition of bacterial growth. Which of the following enzymes is the most likely target of this drug?

- ☐ A. DNA polymerase I
- ☐ B. DNA polymerase III
- ☐ C. Gyrase
- ☐ D. Helicase
- ☐ E. Ligase
- ☐ F. Primase

Submit





A pharmaceutical researcher develops a novel **antibacterial** drug that works by inhibiting **exonuclease activity** during **DNA replication**. When actively dividing *Escherichia coli* is exposed to the drug, enzyme-mediated nucleotide removal in the 5' to 3' direction is impaired, leading to inhibition of bacterial growth. Which of the following enzymes is the most likely target of this drug?

- ☒ A. DNA polymerase I (58%)
- ☐ B. DNA polymerase III (28%)
- ☐ C. Gyrase (3%)
- ☐ D. Helicase (2%)
- ☐ E. Ligase (3%)
- ☐ F. Primase (3%)

Correct



58%
Answered correctly



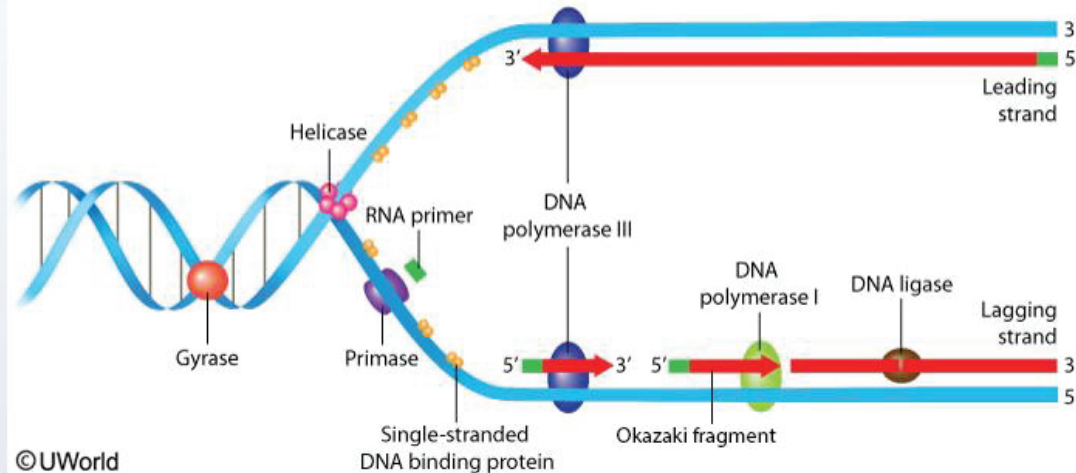
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01/12/2021
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Prokaryotic DNA replication fork



DNA polymerases are the primary enzymes responsible for DNA synthesis, which occurs in the 5' to 3' direction. **Prokaryotes** such as *Escherichia coli* have 3 major DNA polymerases: I, II, and III. DNA replication requires a high degree of fidelity to preserve the genetic code in daughter cells and prevent potentially lethal mutations. This high-fidelity replication is accomplished by the 3' to 5' "proofreading"



direction. **Prokaryotes** such as *Escherichia coli* have 3 major DNA polymerases: I, II, and III. DNA replication requires a high degree of fidelity to preserve the genetic code in daughter cells and prevent potentially lethal mutations. This high-fidelity replication is accomplished by the 3' to 5' "proofreading" exonuclease activity of all 3 DNA polymerases.

DNA polymerase I is unique as it is the only prokaryotic polymerase that also has **5' to 3' exonuclease activity**. This activity functions to **remove the RNA primer** created by RNA primase and **repair damaged DNA** sequences.

(Choice B) DNA polymerase III has 5' to 3' polymerase and 3' to 5' exonuclease activity; however, it does not possess 5' to 3' exonuclease activity.

(Choice C) The enzyme topoisomerase II, also known as DNA gyrase in prokaryotes, relieves tension created during DNA strand unwinding by introducing negative supercoils into the circular DNA. Fluoroquinolones (eg, ciprofloxacin) are a class of antibiotics that work by inhibiting DNA gyrase.

(Choice D) Before DNA replication begins, helicase unwinds the DNA double helix, facilitating separation of the 2 DNA strands by single-stranded DNA-binding proteins.

(Choice E) Okazaki fragments of the lagging strand are bound together by the enzyme ligase.

(Choice F) DNA polymerases cannot begin synthesizing complementary DNA on a single stranded





(Choice C) The enzyme topoisomerase II, also known as DNA gyrase in prokaryotes, relieves tension

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Fluoroquinolones (eg, ciprofloxacin) are a class of antibiotics that work by inhibiting DNA gyrase.

(Choice D) Before DNA replication begins, helicase unwinds the DNA double helix, facilitating separation of the 2 DNA strands by single-stranded DNA-binding proteins.

(Choice E) Okazaki fragments of the lagging strand are bound together by the enzyme ligase.

(Choice F) DNA polymerases cannot begin synthesizing complementary DNA on a single-stranded template without an RNA primer. Primase is an RNA polymerase that synthesizes this primer, which is made up of short stretches of RNA base paired to the DNA template.

Educational objective:

In prokaryotes, DNA polymerase I has 5' to 3' exonuclease activity in addition to 5' to 3' polymerase and 3' to 5' exonuclease activities. This 5' to 3' exonuclease activity functions to remove the RNA primer created by RNA primase and repair damaged DNA sequences.

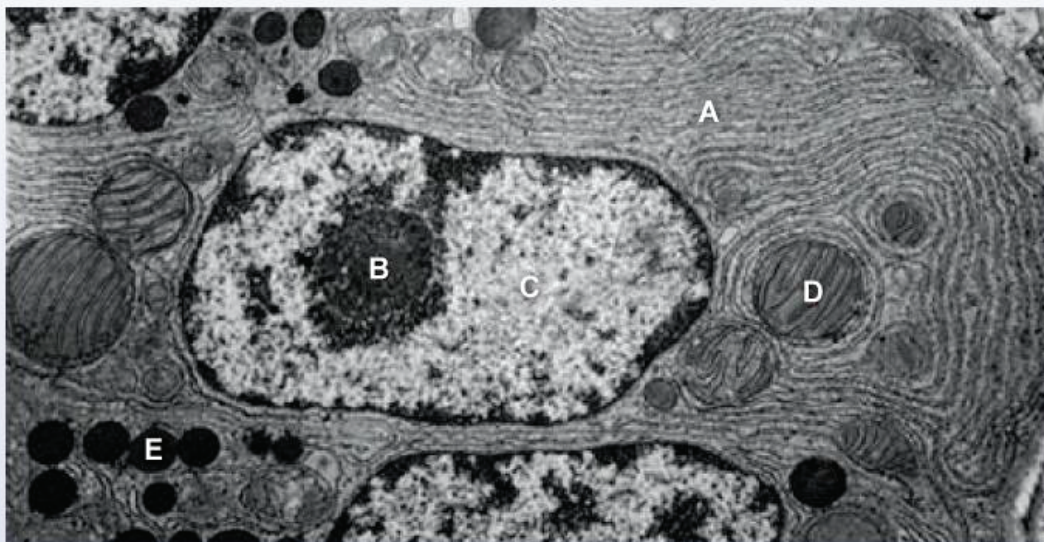
References

- [DNA replication fidelity in Escherichia coli: a multi-DNA polymerase affair.](#)





Molecular biologists are investigating the functional significance of non-coding RNA molecules. During an experiment, they isolate large complexes containing both protein and RNA from exocrine pancreatic cells. The complexes are found both freely floating in the cytoplasm and bound to the endoplasmic reticulum. The RNA found within these complexes is primarily synthesized at which of the following intracellular sites?



☐ A.A





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



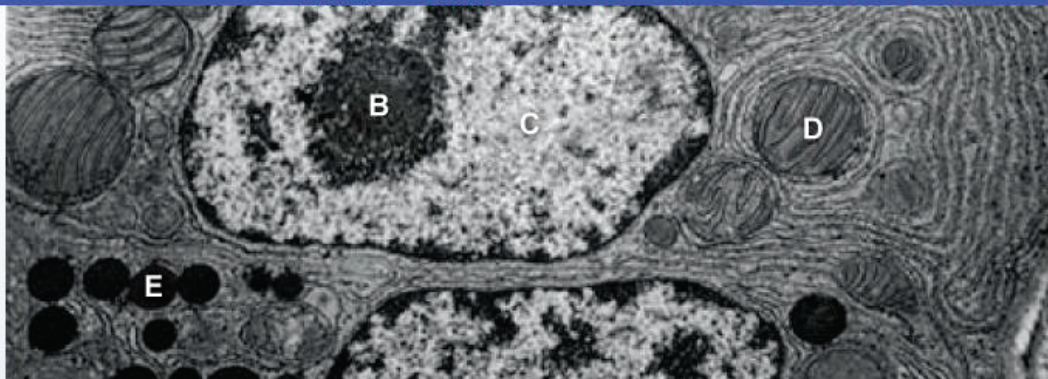
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☐ A.A

☐ B.B

☐ C.C

☐ D.D

☒ E.E

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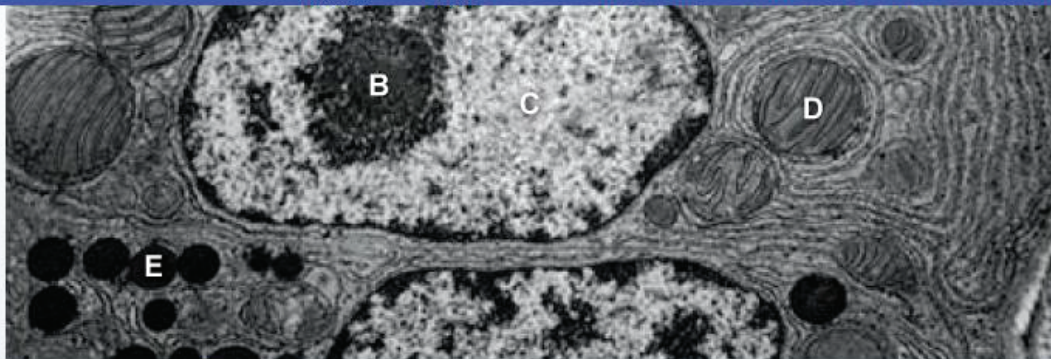
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- ☐ A.A (10%)
- ☒ B.B (54%)
- ☐ C.C (23%)
- ☐ D.D (8%)
- ☐ E.E (3%)

Correct



54%



01 min, 51 secs

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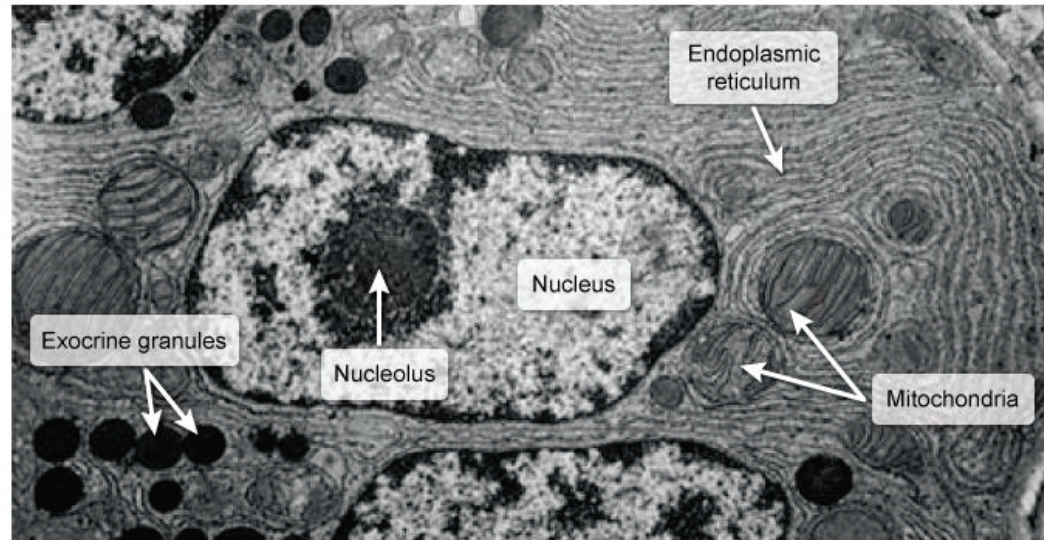


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Cellular organelles under electron microscopy



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The large complexes containing both protein and RNA that are found freely floating and bound to the endoplasmic reticulum are most likely **ribosomes**. Ribosome biogenesis occurs primarily within the **nucleolus**, a dense **round structure** inside the nucleus that is in direct contact with the rest of the



The large complexes containing both protein and RNA that are found freely floating and bound to the endoplasmic reticulum are most likely **ribosomes**. Ribosome biogenesis occurs primarily within the **nucleolus**, a dense **round structure** inside the nucleus that is in direct contact with the rest of the nucleoplasm. The nucleolus contains ribosomal DNA coding for the 28S, 5.8S, and 18S ribosomal RNA (rRNA) components, and it is here where most of the **rRNA is transcribed**. After synthesis, rRNA is combined with ribosomal protein components that are translated in the cytoplasm and then imported into the nucleus. The immature 60S and 40S ribosomal subunits are then exported from the nucleus to fully mature in the cytoplasm.

(Choice A) The rough endoplasmic reticulum is identifiable due to its characteristic long, folded membranes that are coated with ribosomes, giving it a speckled or rough appearance.

(Choice C) The nucleus is identifiable as a membrane-bound structure that contains the nucleolus, electron-lucent euchromatin, and electron-dense heterochromatin (condensed DNA typically found around the periphery). However, most of the ribosomal DNA is found in the form of tandem repeats within the nucleolus; only the 5S rRNA is transcribed outside of the nucleolus.

(Choice D) Mitochondria are organelles with dual phospholipid bilayer membranes that can be recognized by the presence of foldings (ie, cristae) in their inner membranes. Mitochondria have their own ribosomes, but they are typically found within the mitochondrial matrix or bound to the inner mitochondrial membrane.





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(Choice D) Mitochondria are organelles with dual phospholipid bilayer membranes that can be recognized by the presence of foldings (ie, cristae) in their inner membranes. Mitochondria have their own ribosomes, but they are typically found within the mitochondrial matrix or bound to the inner mitochondrial membrane.

(Choice E) Pancreatic zymogen granules are electron-dense structures containing digestive proenzymes that are released from the cell via exocytosis.

Educational objective:

The nucleolus is a dense intranuclear body visible by light and electron microscopy that functions as the primary site of ribosome synthesis and assembly. All ribosomal RNA except 5S rRNA is transcribed in the nucleolus.

Genetics

Genetics (General Principles)

Rna structure & function

Subject

System

Topic

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A healthy couple, who recently emigrated from Eastern Europe, bring their 3-year-old son to the office for evaluation of an eczematous rash. On examination, the child also shows signs of intellectual disability and gait abnormality and has a musty body odor. What is the likelihood that this couple's next child will be affected with the same disease?

- ☐ A. Same as the general population
- ☐ B. 1/32
- ☐ C. 1/16
- ☐ D. 1/8
- ☐ E. 1/4
- ☐ F. 1/2

Submit



A healthy couple, who recently emigrated from Eastern Europe, bring their 3-year-old son to the office for evaluation of an **eczematous rash**. On examination, the child also shows signs of intellectual disability and gait abnormality and has a **musty body odor**. What is the likelihood that this couple's next child will be affected with the same disease?

- ☐ A. Same as the general population (4%)
- ☐ B. 1/32 (0%)
- ☐ C. 1/16 (3%)
- ☐ D. 1/8 (4%)
- ☒ E. 1/4 (82%)
- ☐ F. 1/2 (4%)

Correct



82%
Answered correctly

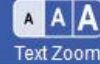
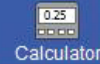
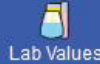


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Intellectual disability, gait or posture abnormality, eczema, and a musty body odor are signs of phenylketonuria (PKU). PKU is an autosomal recessive disease caused by mutation of the gene that codes for phenylalanine hydroxylase. In the United States, phenylalanine levels are measured in all neonates to screen for PKU.

Because PKU is inherited in an autosomal recessive fashion, both of the healthy parents must be heterozygous carriers of the mutation. The probability that their next child will inherit the disease is:

p_1 = probability that the mother transmits the mutant allele = $1/2$

p_2 = probability that the father transmits the mutant allele = $1/2$

The probability that a child will inherit a mutant allele from each carrier parent is equal to $p_1 \times p_2 = 1/4$, as these are independent events.

Educational objective:

Intellectual disability, gait or posture abnormality, eczema, and a musty body odor in a toddler are signs of phenylketonuria (PKU). Most infants with PKU are born to 2 heterozygous carrier parents. The probability that heterozygous carrier parents will transmit an autosomal recessive disease such as PKU to a child is





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



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phenylketonuria (PKU). PKU is an autosomal recessive disease caused by mutation of the gene that codes for phenylalanine hydroxylase. In the United States, phenylalanine levels are measured in all neonates to screen for PKU.

Because PKU is inherited in an autosomal recessive fashion, both of the healthy parents must be heterozygous carriers of the mutation. The probability that their next child will inherit the disease is:

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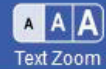
p_2 = probability that the father transmits the mutant allele = $1/2$

The probability that a child will inherit a mutant allele from each carrier parent is equal to $p_1 \times p_2 = 1/4$, as these are independent events.

Educational objective:

Intellectual disability, gait or posture abnormality, eczema, and a musty body odor in a toddler are signs of phenylketonuria (PKU). Most infants with PKU are born to 2 heterozygous carrier parents. The probability that heterozygous carrier parents will transmit an autosomal recessive disease such as PKU to a child is $1/4$.





A series of experiments is being conducted to determine the structure and function of different types of bacterial RNA. Cultures of *Staphylococcus aureus* are exposed to chemicals that lyse the bacterial cells, and the RNA molecules are then extracted. A specific RNA consisting of 90 nucleotides is purified for further analysis. It is found to contain high amounts of chemically modified bases such as dihydrouridine, pseudouridine, and ribothymidine, and its secondary structure arises from base pairing within the chain. Which of the following is the most likely composition of the 3'-end of this molecule?

- ☐ A. AUG
- ☐ B. CCA
- ☐ C. Methylguanosine triphosphate
- ☐ D. Poly-A
- ☐ E. TATA
- ☐ F. UAG

Submit





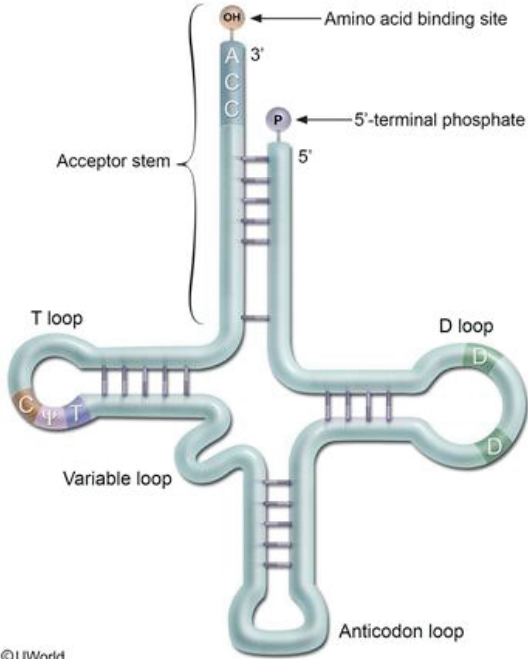
A series of experiments is being conducted to determine the structure and function of different types of **bacterial RNA**. Cultures of *Staphylococcus aureus* are exposed to chemicals that lyse the bacterial cells, and the RNA molecules are then extracted. A specific RNA consisting of **90 nucleotides** is purified for further analysis. It is found to contain high amounts of chemically modified bases such as dihydrouridine, pseudouridine, and ribothymidine, and its secondary structure arises from base pairing within the chain. Which of the following is the most likely composition of the 3'-end of this molecule?

- ☐ A. AUG (5%)
- ☒ B. CCA (41%)
- ☐ C. Methylguanosine triphosphate (5%)
- ☐ D. Poly-A (30%)
- ☐ E. TATA (3%)
- ☐ F. UAG (12%)



Exhibit Display

Secondary structure of tRNA



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Transfer RNA (tRNA) is a form of non-coding RNA composed of 74-93 nucleotides. Specific tRNAs transfer certain amino acid residues to the growing polypeptide during translation. tRNA functions by recognizing the 3 base codon on the mRNA being translated through its anticodon region, which contains complementary bases. The secondary structure of tRNA resembles a cloverleaf and contains the following regions:

- The **acceptor stem** is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. The CCA tail hangs off the 3' end, with the amino acid bound to the 3' terminal hydroxyl group. tRNA is "loaded" with the appropriate amino acid by aminoacyl tRNA synthetase. The acceptor stem helps mediate correct tRNA recognition by the proper aminoacyl tRNA synthetase.
- A **3' CCA tail** is added to the 3' end of tRNA as a posttranscriptional modification in eukaryotes and most prokaryotes. Several enzymes utilize this tail to help recognize tRNA molecules.
- The **D loop** contains numerous dihydrouridine residues, which are modified bases often present in tRNA. The D loop (along with the acceptor stem and anticodon loop) facilitates correct tRNA recognition by the proper aminoacyl tRNA synthetase.





- The **anticodon loop** contains sequences that are complementary to the mRNA codon. During translation, the ribosome complex selects the proper tRNA based solely on its anticodon sequence.
- The **T loop** contains the T Ψ C sequence that is necessary for binding of tRNA to ribosomes. The T Ψ C sequence refers to the presence of ribothymidine, pseudouridine, and cytidine residues.

(Choices A and F) AUG and UAG are mRNA start and stop codons that initiate and terminate translation, respectively.

(Choices C and D) After transcription, eukaryotic pre-mRNA undergoes posttranscriptional modification, which includes the addition of a poly-A tail at the 3' end and methylguanosine cap at the 5' end, and the removal of introns.

(Choice E) A TATA box is an upstream promoter region associated with some genes in eukaryotic organisms. TATA binding protein binds to this promoter during transcription, unwinding the DNA and initiating separation of the strands.

Educational objective:

Transfer RNA (tRNA) is a small, noncoding form of RNA that contains chemically modified bases (eg, dihydrouridine, ribothymidine, pseudouridine). tRNA has a CCA sequence at its 3'-end that is used as a



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Educational objective:

Transfer RNA (tRNA) is a small, noncoding form of RNA that contains chemically modified bases (eg, dihydrouridine, ribothymidine, pseudouridine). tRNA has a CCA sequence at its 3'-end that is used as a recognition sequence by proteins. The 3' terminal hydroxyl group of the CCA tail serves as the amino acid binding site.

References

- CCA addition to tRNA: implications for tRNA quality control.





A genetic researcher is comparing the DNA replication process of prokaryotic and eukaryotic cells. In an experiment, *Escherichia coli* and human cells are cultured in separate media containing tagged nucleotides and their rates of DNA replication are determined. Although the eukaryotic genome is significantly larger and more complex than that of the prokaryote, eukaryotic DNA replication still occurs in a timely manner. Which of the following features of eukaryotic replication best explains this observation?

- ☐ A. Continuous synthesis of the lagging strand
- ☐ B. Energy-independent DNA unwinding
- ☐ C. Multiple origins of replication
- ☐ D. No proofreading of daughter strands
- ☐ E. No requirement for RNA primers

Submit






A genetic researcher is comparing the DNA replication process of prokaryotic and eukaryotic cells. In an experiment, *Escherichia coli* and human cells are cultured in separate media containing tagged nucleotides and their rates of DNA replication are determined. Although the eukaryotic genome is significantly larger and more complex than that of the prokaryote, eukaryotic DNA replication still occurs in a timely manner. Which of the following features of eukaryotic replication best explains this observation?

- ☐ A. Continuous synthesis of the lagging strand (5%)
- ☐ B. Energy-independent DNA unwinding (2%)
- ☒ C. Multiple origins of replication (89%)
- ☐ D. No proofreading of daughter strands (0%)
- ☐ E. No requirement for RNA primers (1%)

Correct

 89%
Answered correctly

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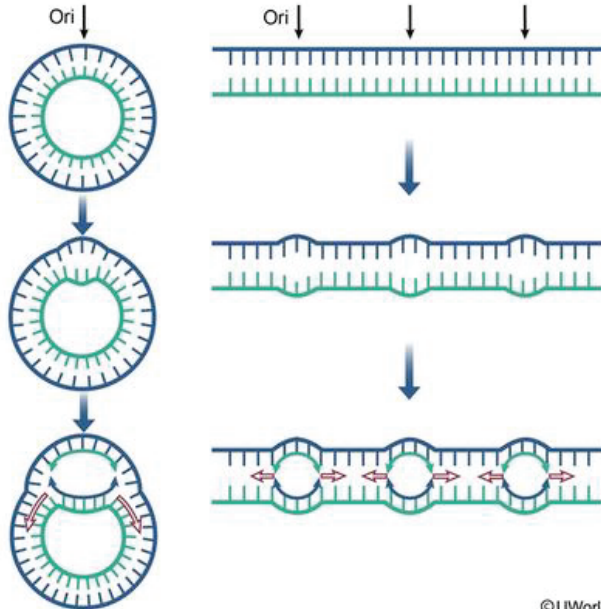
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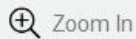
Origin of replication (Ori)

Prokaryotes

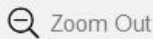
Eukaryotes



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The key steps of DNA replication are similar in eukaryotes and prokaryotes (eg, *Escherichia coli*) and are as follows:

1. Unwinding of double-stranded DNA by helicase to produce single-stranded DNA
2. Formation of a replication fork
3. Synthesis of RNA primers by the enzyme primase
4. Synthesis and concurrent proofreading of daughter DNA strands by DNA polymerases
5. Removal and replacement of RNA primers with DNA
6. Ligation of Okazaki fragments on lagging strands by the enzyme ligase

Despite the similarities of prokaryotic and eukaryotic DNA replication, there are important differences between these processes. Prokaryotes possess 3 major **DNA polymerases** (I, II, and III), whereas eukaryotes have 5 major DNA polymerases (α , β , γ , δ , and ϵ). The **eukaryotic genome** is also much larger and more complex than the prokaryotic genome, which can be partly explained by the abundance of noncoding DNA regions (introns) located between coding regions (exons). In addition, prokaryotes typically have circular DNA with a single origin of replication, whereas eukaryotes have linear DNA with **multiple origins of replication**. This feature allows the eukaryotic genome to be copied in a quick and





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

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Function of prokaryotic & eukaryotic DNA polymerases		
Organism	DNA polymerase	Function
Prokaryote	I	<ul style="list-style-type: none">Removes & replaces RNA primer with DNAProofreads DNA
	II	<ul style="list-style-type: none">Repairs DNAProofreads DNA
	III	<ul style="list-style-type: none">Leading & lagging strand DNA synthesisProofreads DNA
Eukaryote	α	<ul style="list-style-type: none">Synthesizes RNA primerInitiates DNA synthesis
	β	<ul style="list-style-type: none">Repairs DNA
	γ	<ul style="list-style-type: none">Replicates mitochondrial DNAProofreads DNA
	δ	<ul style="list-style-type: none">Elongates Okazaki fragmentsProofreads DNA
	ϵ	<ul style="list-style-type: none">Elongates leading strandProofreads DNA

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noncoding DNA regions (introns) located between coding regions (exons). In addition, prokaryotes

typically have circular DNA with a single origin of replication, whereas eukaryotes have linear DNA with **multiple origins of replication**. This feature allows the eukaryotic genome to be copied in a quick and effective manner despite its large size.

(Choice A) Eukaryotic and prokaryotic DNA polymerases synthesize daughter strand DNA in the 5' to 3' direction. The leading strand is formed continuously, whereas the lagging strand is formed discontinuously, creating Okazaki fragments.

(Choice B) DNA unwinding is an energy-dependent process performed by the enzyme helicase in both prokaryotes and eukaryotes.

(Choice D) Proofreading of daughter strands during DNA replication is necessary to preserve the genetic code and prevent potentially lethal mutations. All 3 prokaryotic DNA polymerases and most eukaryotic DNA polymerases (eg, γ , δ , ϵ) possess 3' to 5' exonuclease ("proofreading") activity.

(Choice E) Prokaryotic and eukaryotic DNA polymerases require an RNA primer before they can initiate synthesis of complementary DNA on a single-stranded template. Primase (prokaryotes) and DNA polymerase α (eukaryotes) are the enzymes responsible for synthesizing this primer.

Educational objective:





creating Okazaki fragments.

(Choice B) DNA unwinding is an energy-dependent process performed by the enzyme helicase in both prokaryotes and eukaryotes.

(Choice D) Proofreading of daughter strands during DNA replication is necessary to preserve the genetic code and prevent potentially lethal mutations. All 3 prokaryotic DNA polymerases and most eukaryotic DNA polymerases (eg, γ , δ , ϵ) possess 3' to 5' exonuclease ("proofreading") activity.

(Choice E) Prokaryotic and eukaryotic DNA polymerases require an RNA primer before they can initiate synthesis of complementary DNA on a single-stranded template. Primase (prokaryotes) and DNA polymerase α (eukaryotes) are the enzymes responsible for synthesizing this primer.

Educational objective:

Multiple origins of replication make eukaryotic DNA replication quick and effective despite the large size and complexity of the genome compared to that of prokaryotic organisms.

References

- [Mechanism of chromosomal DNA replication initiation and replication fork stabilization in eukaryotes.](#)

Genetics

Genetics (General Principles)

Dna replication





A 4-year-old boy is brought to the physician for fatigue and persistent bone pain. Physical examination shows diffuse lymphadenopathy and multiple purpura over his arms and legs. Laboratory analysis reveals anemia and thrombocytopenia, and a peripheral blood smear shows lymphoblasts. After further workup, he is diagnosed with acute lymphoblastic leukemia and started on a chemotherapy regimen that includes doxorubicin. This agent intercalates between DNA base pairs and inhibits DNA replication, a process that normally occurs at sites known as replication forks. As the replication forks move across the DNA molecule, 2 distinct daughter strands are formed. Which of the following is unique to the daughter strand that is synthesized in the opposite direction of the growing replication fork?

- ☐ A. Synthesis of multiple, short DNA fragments
- ☐ B. 5'→3' exonuclease activity of DNA polymerase
- ☐ C. 3'→5' exonuclease activity of DNA polymerase
- ☐ D. 3'→5' polymerase activity of DNA polymerase
- ☐ E. RNA primer synthesis before DNA strand synthesis





shows diffuse lymphadenopathy and multiple purpura over his arms and legs. Laboratory analysis reveals anemia and thrombocytopenia, and a peripheral blood smear shows lymphoblasts. After further workup, he is diagnosed with acute lymphoblastic leukemia and started on a chemotherapy regimen that includes doxorubicin. This agent intercalates between DNA base pairs and inhibits DNA replication, a process that normally occurs at sites known as replication forks. As the replication forks move across the DNA molecule, 2 distinct daughter strands are formed. Which of the following is unique to the daughter strand that is synthesized in the opposite direction of the growing replication fork?

- ☒ A. Synthesis of multiple, short DNA fragments (75%)
- ☐ B. 5'→3' exonuclease activity of DNA polymerase (6%)
- ☐ C. 3'→5' exonuclease activity of DNA polymerase (8%)
- ☐ D. 3'→5' polymerase activity of DNA polymerase (3%)
- ☐ E. RNA primer synthesis before DNA strand synthesis (5%)

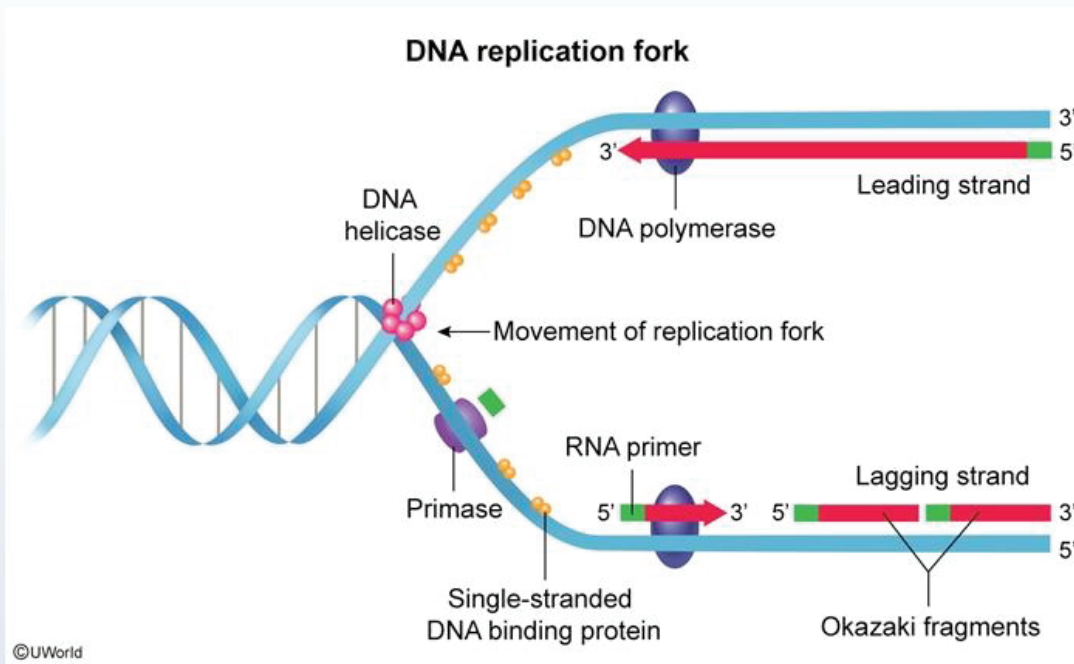
Correct

75%

41 secs

10/07/2020





DNA replication begins at **multiple sites** within eukaryotic chromosomes called origins of replication. At these sites, the parent DNA double helix is separated and unwound in a process facilitated by the helicase enzyme and single-stranded DNA-binding proteins. The locations where unwound DNA meets the double





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

DNA replication begins at **multiple sites** within eukaryotic chromosomes called origins of replication. At these sites, the parent DNA double helix is separated and unwound in a process facilitated by the helicase enzyme and single-stranded DNA-binding proteins. The locations where unwound DNA meets the double helix are known as replication forks. Replication forks travel bidirectionally away from the origin of replication as DNA polymerase synthesizes complementary daughter DNA strands.

Synthesis of the daughter strands occurs simultaneously from both parent strands. Because **DNA synthesis can occur only in the 5'→3' direction**, one daughter strand is synthesized **continuously** toward the replication fork (**leading strand**). However, the other strand must be synthesized **discontinuously** in a direction away from the replication fork (**lagging strand**), with more and more segments being added as the replication fork moves across the DNA double helix. This results in the formation of **Okazaki fragments**, short stretches of newly synthesized DNA that are separated by RNA primers. These primers are removed and replaced with DNA, and the Okazaki fragments are subsequently joined together by DNA ligase.

(Choice B) 5'→3' exonuclease activity is needed during the synthesis of both daughter strands to remove RNA primers (although there are many more primers on the lagging strand, primers must also be removed when joining leading strands from separate origins of replication). In addition, 5'→3' exonuclease activity is necessary to correct DNA replication errors that occur on both strands.





necessary to correct DNA replication errors that occur on both strands.

(Choice C) DNA polymerases have 3'→5' exonuclease activity (proofreading function) that allows them to reverse direction and remove incorrectly placed bases. This process occurs on both newly formed daughter strands to help reduce replication errors.

(Choice D) DNA polymerases do not have 3'→5' polymerase activity; all known polymerases synthesize in the 5'→3' direction.

(Choice E) Before DNA polymerase can initiate DNA synthesis, RNA primers must first be synthesized by the enzyme primase (DNA-dependent RNA polymerase). This process is necessary for synthesis of both daughter strands (even though it occurs much more frequently on the lagging strand).

Educational objective:

DNA synthesis can occur only in the 5'→3' direction. Okazaki fragments are short stretches of newly synthesized DNA that are separated by RNA primers. They are formed by the discontinuous synthesis of DNA on the lagging strand during replication.

References

- Reconstitution of eukaryotic lagging strand DNA replication.
- Timing, coordination, and rhythm: orchestration of the DNA replication fork





A pharmaceutical researcher is evaluating a nuclear enzyme inhibitor for the treatment of an inherited disorder. During an experiment, he extracts and purifies nuclear enzymes from skin cells of an affected patient. One of these enzymes is found to catalyze the methylation of cytosine residues in DNA using S-adenosyl-methionine (SAM) as the methyl donor. This enzyme most likely plays a crucial role in which of the following genetic processes?

- ☐ A. Aneuploidy
- ☐ B. Epistasis
- ☐ C. Imprinting
- ☐ D. Meiotic nondisjunction
- ☐ E. Pleiotropy


Submit




A pharmaceutical researcher is evaluating a nuclear enzyme inhibitor for the treatment of an inherited disorder. During an experiment, he extracts and purifies nuclear enzymes from skin cells of an affected patient. One of these enzymes is found to catalyze the methylation of cytosine residues in DNA using S-adenosyl-methionine (SAM) as the methyl donor. This enzyme most likely plays a crucial role in which of the following genetic processes?

- ☐ A. Aneuploidy (4%)
- ☐ B. Epistasis (7%)
- ☒ C. Imprinting (73%)
- ☐ D. Meiotic nondisjunction (5%)
- ☐ E. Pleiotropy (8%)

Correct

 73%
Answered correctly

 01 min, 32 secs
Time Spent

 02/14/2021
Last Updated





DNA methylation refers to the addition of methyl groups to nucleotide residues (often adenine and cytosine) by **DNA methyltransferase**, an enzyme that uses S-adenosyl-methionine (SAM) as the methyl group donor.

DNA methylation is an epigenetic process by which eukaryotic organisms modify gene expression without altering the genetic code. For example, methylation of cytosine-guanine dinucleotide repeats (CpGs) in the promoter region of genes effectively silences transcription of those genes. Fragile X syndrome is an X-linked disorder caused by an increased number of CGG trinucleotide repeats on the fragile X mental retardation 1 (*FMR1*) gene, leading to hypermethylation of cytosine residues and *FMR1* inactivation.

Cytosine methylation is also used in **genomic imprinting**, a phenomenon in which an offspring's genes are expressed in a parent-specific manner. For instance, an allele inherited from the father may be inactivated or "imprinted" by methylation so that only the allele from the mother is expressed.

(Choices A and D) Aneuploidy refers to the presence of an abnormal number of chromosomes and is the result of chromosomal nondisjunction during mitosis or meiosis.

(Choice B) Epistasis is a phenomenon in which the allele of one gene affects the phenotypic expression of alleles in another gene.





are expressed in a parent-specific manner. For instance, an allele inherited from the father may be inactivated or "imprinted" by methylation so that only the allele from the mother is expressed.

(Choices A and D) Aneuploidy refers to the presence of an abnormal number of chromosomes and is the result of chromosomal nondisjunction during mitosis or meiosis.

(Choice B) Epistasis is a phenomenon in which the allele of one gene affects the phenotypic expression of alleles in another gene.

(Choice E) Pleiotropy refers to the phenomenon in which a single gene influences multiple phenotypic traits.

Educational objective:

Genomic imprinting refers to the phenomenon in which an offspring's genes are expressed in a parent-specific manner. Genomic imprinting is caused by DNA methylation, an epigenetic process in which genes can be silenced by attaching methyl groups to cytosine residues in the DNA molecule.

References

- [Mammalian Genomic Imprinting.](#)





A 6-year-old boy is brought to the office due to a persistent facial ulcer for the past 2 months. His mother reports that the patient has extreme sensitivity to sunlight and has developed freckles on his face, neck, and limbs since infancy. On physical examination, the skin in sun-exposed areas is dry and rough with numerous freckles and erythematous macules. There is an ulcerated plaque on the left face; a biopsy reveals squamous cell carcinoma. Further testing leads to a diagnosis of xeroderma pigmentosum. A defect in which of the following enzymes is most likely causing this patient's condition?

- ☐ A. 3'→5' exonuclease
- ☐ B. DNA ligase
- ☐ C. Endonuclease
- ☐ D. Helicase
- ☐ E. Topoisomerase

Submit





A 6-year-old boy is brought to the office due to a persistent **facial ulcer** for the past 2 months. His mother reports that the patient has extreme sensitivity to sunlight and has developed freckles on his face, neck, and limbs since infancy. On physical examination, the skin in sun-exposed areas is dry and rough with numerous freckles and erythematous macules. There is an ulcerated plaque on the left face; a biopsy reveals squamous cell carcinoma. Further testing leads to a diagnosis of xeroderma pigmentosum. A defect in which of the following enzymes is most likely causing this patient's condition?

- ☐ A. 3'→5' exonuclease (33%)
- ☐ B. DNA ligase (4%)
- ☒ C. Endonuclease (58%)
- ☐ D. Helicase (0%)
- ☐ E. Topoisomerase (2%)

Correct



58%
Answered correctly



55 secs
Time Spent



02/26/2021
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Previous



Next



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Lab Values



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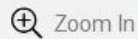
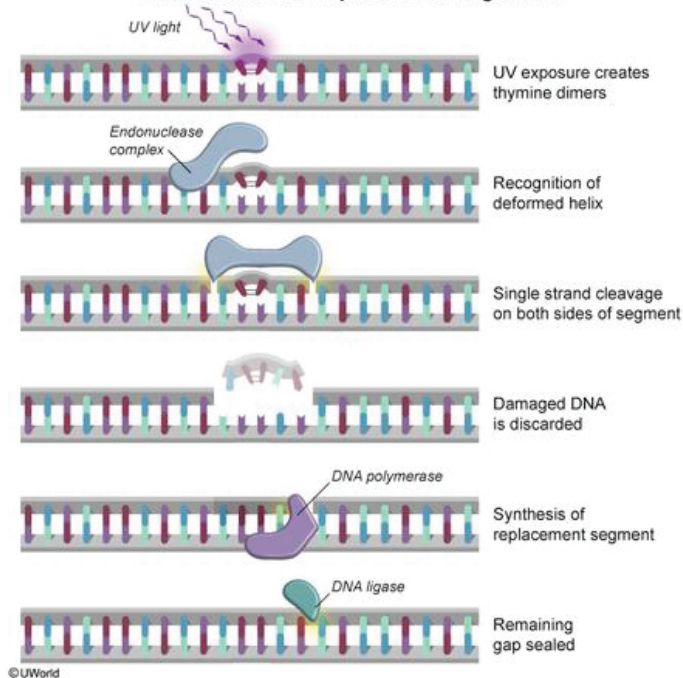


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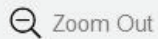
Nucleotide excision repair of UV damaged DNA

Exhibit Display

Nucleotide excision repair of UV damaged DNA



Zoom In



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Reset



New



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Synthesis of

Block Time Remaining: 00:25:42

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End Block



This boy with severe photosensitivity, poikiloderma, hyperpigmentation in sun-exposed areas, and squamous cell carcinoma of the skin has **xeroderma pigmentosum**, an autosomal recessive disorder characterized by defects in **nucleotide excision repair**.

DNA can be damaged by **ultraviolet rays**, leading to formation of **thymine dimers** between 2 adjacent thymine residues. These thymine dimers are repaired by **UV-specific endonuclease**, an enzyme that is frequently deficient in patients with xeroderma pigmentosum. This enzyme recognizes distortions in the structure of DNA caused by thymine dimers and subsequently excises stretches of single-stranded DNA that contain these defects. The gap created following this excision is then filled by DNA polymerase, which uses the opposite DNA strand as a template. The new strand of DNA is then joined on both ends to the existing DNA by the enzyme ligase.

(Choice A) 3'→5' exonuclease activity describes the "proofreading" ability of DNA polymerase. This ability allows for the recognition and repair of mismatched bases during DNA replication. Hereditary nonpolyposis colon cancer is associated with DNA mismatch repair gene mutations.

(Choice B) DNA ligase is responsible for creating a phosphodiester linkage between the phosphate group of the 5' end of a DNA fragment and the hydroxyl group of the 3' end. DNA ligase is particularly active in joining the Okazaki fragments created during discontinuous replication of the lagging strand.





(Choice C) DNA ligase is responsible for creating a phosphodiester linkage between the phosphate group

of the 5' end of a DNA fragment and the hydroxyl group of the 3' end. DNA ligase is particularly active in joining the Okazaki fragments created during discontinuous replication of the lagging strand.

(Choice D) Helicases are responsible for unwinding and separating double-stranded DNA into single-stranded DNA in preparation for DNA replication.

(Choice E) Topoisomerase enzymes relieve DNA supercoiling produced during unwinding and separation by helicase. Prokaryotic topoisomerase II (DNA gyrase) is inhibited by fluoroquinolone antibiotics, whereas eukaryotic topoisomerase II is inhibited by the anticancer drug etoposide.

Educational objective:

Xeroderma pigmentosum is an autosomal recessive disorder characterized by defective nucleotide excision repair often caused by a deficiency in UV-specific endonuclease. Affected children usually have severe photosensitivity, hyperpigmentation in sun-exposed areas, and a greatly increased risk for skin cancer.

References

- [Xeroderma pigmentosum.](#)

Genetics

Genetics (General Principles)

Xeroderma pigmentosum





A 56-year-old man comes to the office due to difficulty swallowing for the past several months. He has the most trouble with solid foods and says, "They seem to get stuck in my throat if I don't chew a lot." The patient has no chest pain or heartburn and has lost 4.5 kg (10 lb) in the last 3 months. He has been an avid hunter for many years and frequently cures the meat he eats with sodium nitrite. Physical examination is unremarkable. Endoscopy shows an ulcerated mass in the distal third of the esophagus, and biopsy samples are obtained from the mass and adjacent normal mucosa. Analysis of the samples shows accelerated cytosine deamination of chromosomal DNA in both normal and malignant epithelial cells. This damage is most likely to be repaired through which of the following enzymatic sequences?

- ☐ A. Endonuclease, polymerase, glycosylase, lyase, ligase
- ☐ B. Endonuclease, polymerase, lyase, glycosylase, ligase
- ☐ C. Glycosylase, endonuclease, lyase, polymerase, ligase
- ☐ D. Glycosylase, ligase, lyase, endonuclease, polymerase
- ☐ E. Lyase, endonuclease, glycosylase, polymerase, ligase





most trouble with solid foods and says, "They seem to get stuck in my throat if I don't chew a lot." The patient has no chest pain or heartburn and has lost 4.5 kg (10 lb) in the last 3 months. He has been an avid hunter for many years and frequently cures the meat he eats with sodium nitrite. Physical examination is unremarkable. Endoscopy shows an ulcerated mass in the distal third of the esophagus, and biopsy samples are obtained from the mass and adjacent normal mucosa. Analysis of the samples shows accelerated cytosine deamination of chromosomal DNA in both normal and malignant epithelial cells. This damage is most likely to be repaired through which of the following enzymatic sequences?

- ☐ A. ~~Endonuclease, polymerase, glycosylase, lyase, ligase~~ (15%)
- ☐ B. ~~Endonuclease, polymerase, lyase, glycosylase, ligase~~ (23%)
- ☒ C. Glycosylase, endonuclease, lyase, polymerase, ligase (44%)
- ☐ D. ~~Glycosylase, ligase, lyase, endonuclease, polymerase~~ (1%)
- ☐ E. Lyase, endonuclease, glycosylase, polymerase, ligase (14%)

Correct



44%

Answered correctly



01 min, 56 secs

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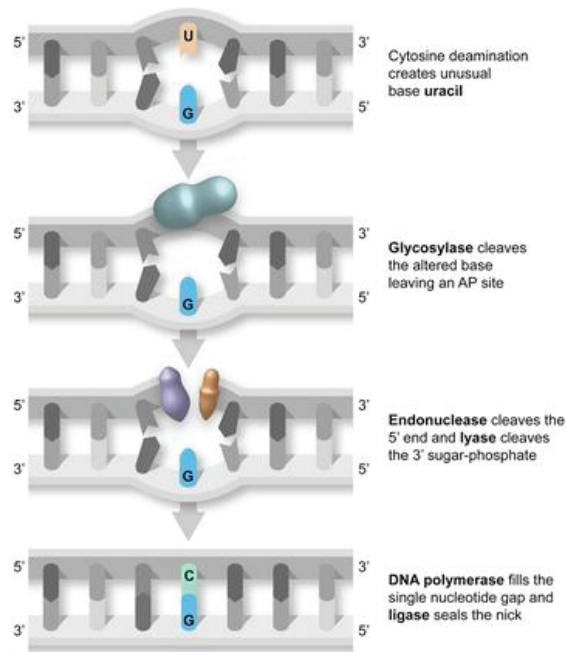


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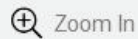


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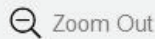
Base excision repair



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Base excision repair is responsible for repairing various non-bulky DNA base alterations, including depurination, alkylation, oxidation, and deamination. Excessive consumption of **dietary nitrites** can promote the deamination of cytosine, adenine, and guanine to form uracil, hypoxanthine, and xanthine, respectively. If these abnormal bases are not removed and replaced with the correct base, DNA mutations and **carcinogenesis** may result.

Base excision repair (not to be confused with nucleotide excision repair or mismatch repair) begins with recognition of abnormal bases by specific **glycosylases**. These cleave the altered DNA bases from the parent DNA molecule, leaving an empty sugar-phosphate site called an apurinic/apyrimidinic site (AP). An **endonuclease** then cleaves the 5' end of the AP site before a **lyase** (or phosphodiesterase) enzyme subsequently completes extraction of the AP site from the DNA molecule by removing the remaining sugar-phosphate group. **DNA polymerase** then fills the gap with the correct sugar-phosphate base, and the final nick is sealed by **ligase**.

Educational objective:

Base excision repair is used to correct single-base DNA defects induced spontaneously or by exogenous chemicals. In this process, glycosylases remove the defective base, and the corresponding empty sugar-



recognition of abnormal bases by specific **glycosylases**. These cleave the altered DNA bases from the parent DNA molecule, leaving an empty sugar-phosphate site called an apurinic/apyrimidinic site (AP). An **endonuclease** then cleaves the 5' end of the AP site before a **lyase** (or phosphodiesterase) enzyme subsequently completes extraction of the AP site from the DNA molecule by removing the remaining sugar-phosphate group. **DNA polymerase** then fills the gap with the correct sugar-phosphate base, and the final nick is sealed by **ligase**.

Educational objective:

Base excision repair is used to correct single-base DNA defects induced spontaneously or by exogenous chemicals. In this process, glycosylases remove the defective base, and the corresponding empty sugar-phosphate site is cleaved and removed by the action of endonuclease and lyase. DNA polymerase then replaces the missing nucleotide, and ligase seals the final remaining nick.

References

- [Overview of base excision repair biochemistry.](#)

Genetics

Genetics (General Principles)

Dna structure & function

Subject

System

Topic

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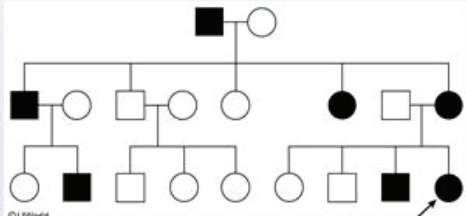
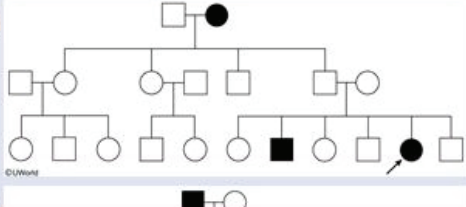


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A 19-year-old woman is evaluated for new onset generalized tonic-clonic seizures. For the past several years, she has also been having erratic jerks of her arms and legs, and intermittent muscle weakness. The girl has multiple family members with similar symptoms. Neurological examination reveals decreased sensation in the lower extremities and a broad-based gait. Skeletal muscle biopsy shows ragged, red-appearing muscle fibers. Further analysis reveals that the patient's symptoms are due to a mutation affecting extranuclear DNA. Which of the following pedigrees is most likely to represent this patient's family history? (The arrow points to the patient.)

☐ A.☐ B.

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Item 22 of 40

Question Id: 11914



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Previous

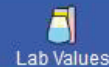
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Full Screen



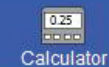
Tutorial



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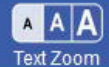
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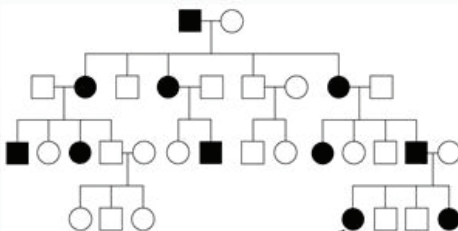


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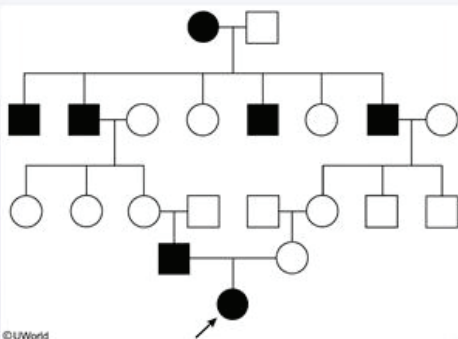


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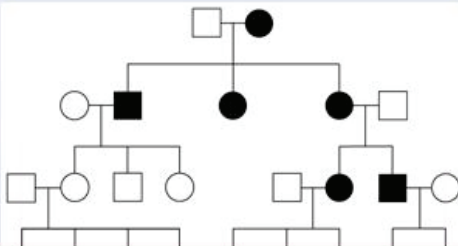
☐ C.



☐ D.



☐ E.



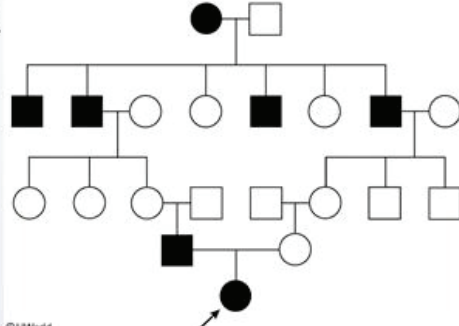
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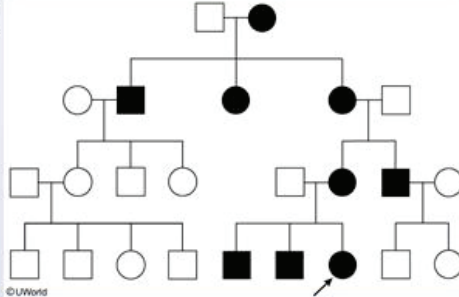




D.



E.

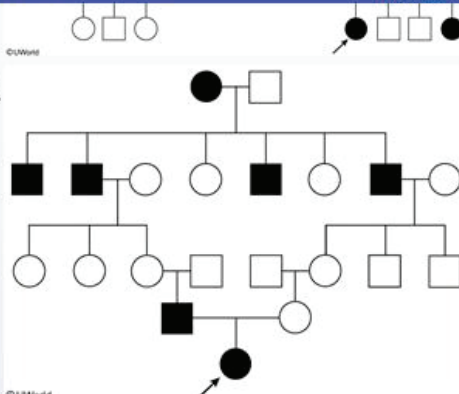


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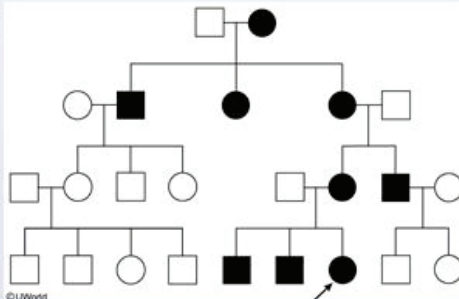


D.



(3%)

✓ E.



(84%)

Correct

84%
Answered correctly01 min, 20 secs
Time Spent03/01/2021
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End Block

This patient most likely has a form of **mitochondrial myopathy**. Without properly functioning mitochondria, cells are unable to use oxidative phosphorylation to efficiently produce adequate levels of ATP. Organ systems such as the brain and skeletal muscle will be affected first due to their high metabolic demand relative to other tissues. Affected patients often present with myopathy (eg, **muscle weakness**, myalgia), lactic acidosis due to impaired aerobic glycolysis, and **nervous system dysfunction** (eg, neuropathy, seizures). Muscle biopsy classically shows **ragged red fibers**.

Mitochondria are unique organelles because they contain their own DNA, known as **mtDNA**. Offspring inherit mtDNA in a maternal fashion with no paternal contribution (**maternal inheritance**). Only affected females transmit abnormal mitochondria to offspring; transmission never occurs through males (even if they are affected).

(Choice A) Autosomal dominant disorders affect 50% of all children (males and females) born to one affected parent. The disease will appear in consecutive generations, and father-to-son transmission can occur.

(Choice B) Autosomal recessive conditions affect about 25% of all children (males and females) with two carrier parents. Offspring of a single affected parent will be carriers for the disorder. As a result, the disease can skip generations, but consanguineous families will show increased incidence.



(Choice B) Autosomal recessive conditions affect about 25% of all children (males and females) with two carrier parents. Offspring of a single affected parent will be carriers for the disorder. As a result, the disease can skip generations, but consanguineous families will show increased incidence.

(Choice C) In **X-linked dominant** disorders, all female children of affected males will have the condition, but both female and male children of an affected female have a 50% chance of being affected. There is no father-to-son transmission.

(Choice D) In **X-linked recessive** conditions, male offspring of a carrier female have a 50% chance of being affected, whereas female offspring have a 50% chance of being carriers. Female children of an affected father are obligate carriers. The disease can skip generations, and there is no father-to-son transmission.

Educational objective:

Mitochondrial dysfunction frequently presents with myopathy, nervous system dysfunction, lactic acidosis, and ragged red fibers on muscle biopsy. Mitochondrial myopathies due to mtDNA mutations are inherited solely in a maternal fashion (ie, maternal inheritance). Therefore, transmission occurs only through affected females and never through males.

References





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

(Choice B) Autosomal recessive conditions affect about 25% of all children (males and females) with two

Exhibit Display

X-linked dominant inheritance

Affected father

		Mother			
		X		X	
Father	X _d	XX _d		XX _d	All daughters are affected
	Y	XY		XY	All sons are normal

Affected mother

		Mother			
		X		X _d	
Father	X	XX		XX _d	All sons & daughters have 50% chance of being affected
	Y	XY		X _d Y	

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New | Existing

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Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

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Settings

(Choice B) Autosomal recessive conditions affect about 25% of all children (males and females) with two

Exhibit Display

X-linked recessive inheritance

Affected father

		Mother		
		X	X	
Father	X ^d	XX ^d	XX ^d	All daughters are carriers
	Y	XY	XY	All sons are normal

Carrier mother

		Mother		
		X	X ^d	
Father	X	XX	XX ^d	Daughters have 50% chance of becoming carriers
	Y	XY	X ^d Y	Sons have 50% chance of being affected

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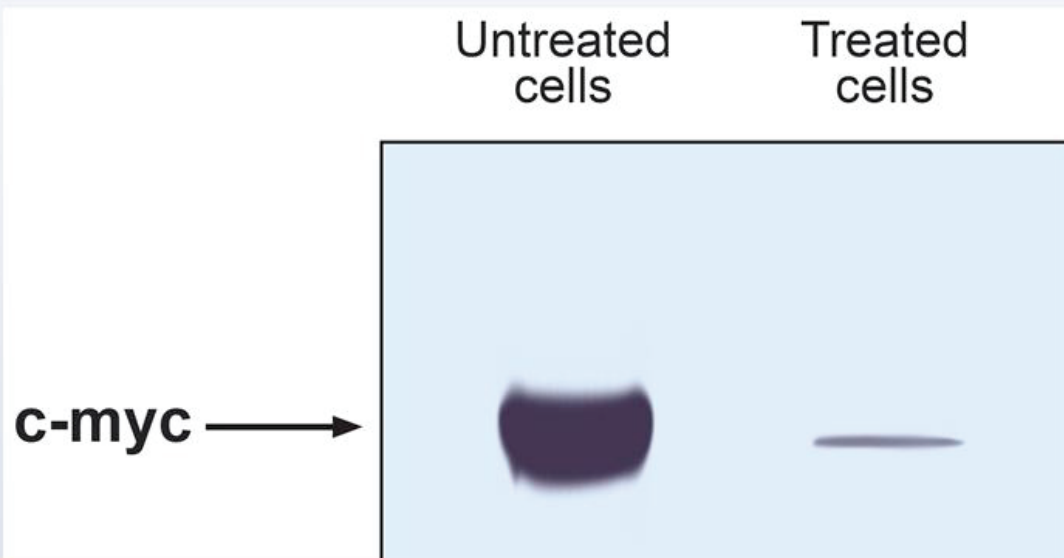
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A pharmaceutical corporation investigating new therapeutic agents for treatment of Burkitt lymphoma synthesizes a double-stranded RNA molecule that is 21 base pairs in length. The RNA molecule has a base pair sequence that is complementary to a region of mRNA encoding c-Myc. Introduction of the RNA molecule into tumor cells results in a significant reduction in cell growth. Western blot analysis of equivalent numbers of treated and untreated cells is shown below.





Item 23 of 40

Question Id: 11595



Mark



Previous



Next



Full Screen



Tutorial



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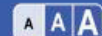
Notes



Calculator



Reverse Color

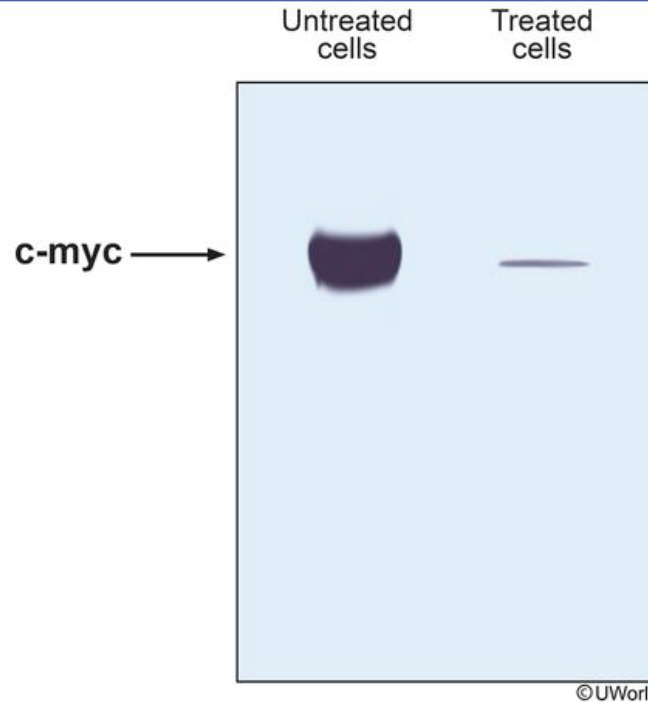


Text Zoom



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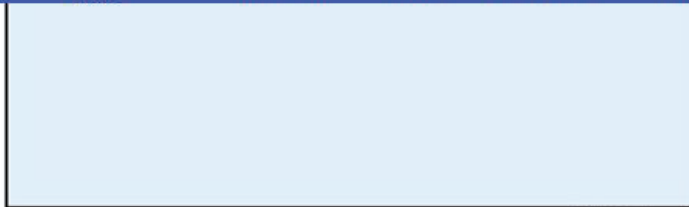
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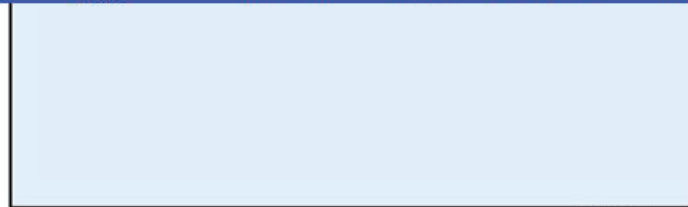


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Which of the following processes was most likely directly interrupted in the cells exposed to the RNA molecule?

- ☐ A. DNA replication
- ☐ B. DNA transcription
- ☐ C. mRNA translation
- ☐ D. Proteasome activity
- ☐ E. Splicing

Submit



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Which of the following processes was most likely directly interrupted in the cells exposed to the RNA molecule?

- ☒ A. DNA replication (8%)
- ☐ B. DNA transcription (17%)
- ☒ C. mRNA translation (64%)
- ☐ D. Proteasome activity (3%)
- ☐ E. Splicing (5%)

Incorrect

Correct answer



64%

Answered correctly



02 mins, 15 secs

Time Spent



10/12/2020

Last Updated

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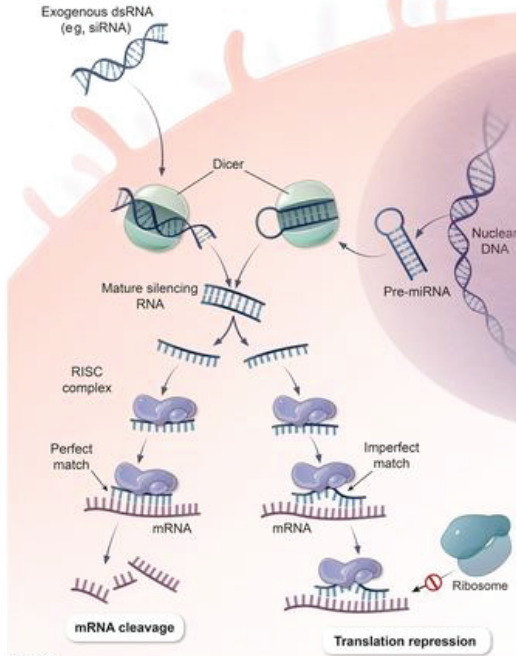


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RNA interference



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The results of the western blot show that the treated cell line produces less c-myc protein. This is most likely due to RNA interference, a mechanism by which short (20-30 base pair) **double-stranded RNA** sequences induce **posttranscriptional gene silencing**.

Silencing RNA includes both small interfering RNA (siRNA) and microRNA (miRNA). The human genome encodes over 1000 miRNA genes, each one capable of repressing hundreds of target genes; altered expression of miRNA genes are involved in the development of many diseases, including hematologic and solid malignancies. In addition, synthetic siRNA sequences can be introduced into cells to silence specific pathogenic genes (eg, c-Myc oncogene) and are being explored as possible **therapeutic agents**.

After being transcribed, miRNA undergoes processing in the nucleus to form a **double-stranded** precursor that is then exported into the cytoplasm. There, the precursor is cleaved into a short RNA helix by a ribonuclease protein called **dicer**. The individual strands are then separated and incorporated into RNA-induced silencing complex (RISC). This multiprotein complex uses its associated miRNA as a template to bind to complementary sequences found on target mRNAs. An exact match generally results in **mRNA degradation**, but a partial match also causes **translational repression** by preventing ribosome and translation factor binding.

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translation factor binding.

(Choice A) DNA polymerase requires a short nucleic acid sequence primer for initiation of DNA synthesis.

During DNA replication, these primers are formed from RNA bases by the enzyme DNA primase.

(Choice B) DNA transcription is the process in which RNA is transcribed from a DNA template by an RNA polymerase enzyme. Although certain miRNA sequences can cause transcriptional inhibition, posttranscriptional silencing is the predominant means of RNA interference.

(Choice D) Degradation of proteins and polypeptides occurs in proteasomes and lysosomes. Proteasomes mainly degrade nuclear and cytoplasmic proteins; lysosomes degrade cellular organelles and extracellular proteins.

(Choice E) Small nuclear RNA (snRNA) molecules bind to specific proteins to form small nuclear ribonucleoproteins (snRNPs). These snRNPs associate with pre-mRNA to form spliceosomes, which function to remove introns from pre-mRNA during processing within the nucleus.

Educational objective:

Short non-coding RNA sequences (eg, microRNA and small interfering RNA) induce posttranscriptional gene silencing by base-pairing with complementary sequences within target mRNA molecules.

References

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Geneticists are studying a malfunctioning protein that causes impaired endothelial cell migration and angiogenesis. They have noticed that the amino acid sequence of the protein is truncated compared to normal controls. The mutated mRNA strand is isolated, and analysis shows a nonsense mutation located near the 3' end of the coding region. The 3' terminal coding sequence of the abnormal mRNA strand is shown below.

Which of the following tRNA anticodons is responsible for adding the last amino acid to the truncated polypeptide during protein translation?

- ☐ A. 5'-AAC-3'
- ☐ B. 5'-AUC-3'
- ☐ C. 5'-CAA-3'
- ☐ D. 5'-GCU-3'
- ☐ E. 5'-UCG-3'

Submit

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Geneticists are studying a malfunctioning protein that causes impaired endothelial cell migration and angiogenesis. They have noticed that the amino acid sequence of the protein is truncated compared to normal controls. The mutated mRNA strand is isolated, and analysis shows a nonsense mutation located near the 3' end of the coding region. The 3' terminal coding sequence of the abnormal mRNA strand is shown below.

5'—ACG—CUA—CCA—UUG—UAA—CAA—GUU—AGC—UAG—3'

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- ☐ B. 5'-AUC-3'
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- ☐ D. 5'-GCU-3'
- ☐ E. 5'-UCG-3'



near the 3' end of the coding region. The 3' terminal coding sequence of the abnormal mRNA strand is shown below.

5'—ACG—CUA—CCA—UUG—UAA—CAA—GUU—AGC—UAG—3'

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Which of the following tRNA anticodons is responsible for adding the last amino acid to the truncated polypeptide during protein translation?

- ☐ A. 5'-AAC-3' (6%)
- ☐ B. 5'-AUC-3' (38%)
- ☒ C. 5'-CAA-3' (32%)
- ☐ D. 5'-GCU-3' (15%)
- ☐ E. 5'-UCG-3' (8%)

Correct

32%



01 min, 49 secs



01/10/2021

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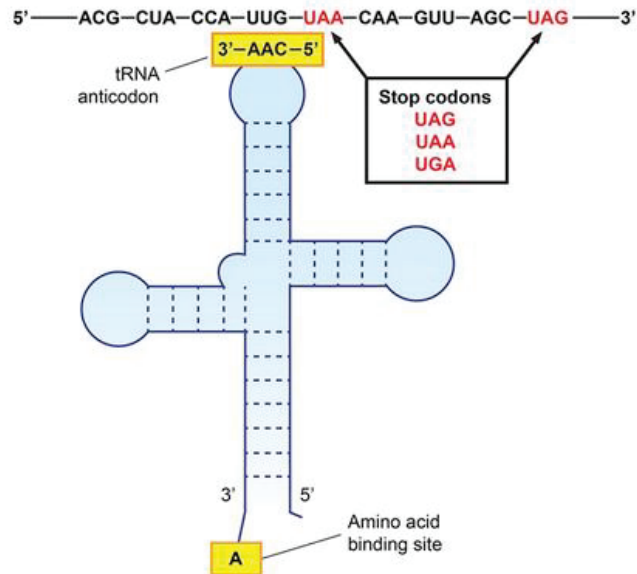


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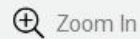


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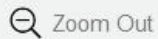
mRNA, tRNA, & stop codons



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One codon (AUG) signals initiation of protein synthesis and 3 codons (**UAA**, **UAG**, and **UGA**) stop protein synthesis. **Stop codons** function only to terminate translation; they do not add amino acids to the polypeptide chain.

Transfer RNA molecules (**tRNA**) transport amino acids to the ribosome and ensure placement of the proper amino acid. One end of the molecule serves as the amino acid binding site; the opposite end contains a specific nucleic acid sequence known as the **anticodon** that is **complementary** to one or more **mRNA codons** (due to base wobbling). The type of amino acid that is bound to each tRNA molecule is determined by its anticodon sequence; this ensures that the proper amino acid is added at each mRNA codon during protein synthesis.

Translation of the mRNA template proceeds in the 5' to 3' direction. The mRNA of the dysfunctional protein in the question stem contains an extra stop codon (UAA) before the normal stop codon (UAG) at the end of the template. During protein translation, the **first stop codon** encountered will **bind a release factor**, halting protein synthesis. Therefore, the codon just prior to the first stop codon will be the last codon to add an amino acid. In this case, (5'-**UUG**-3') is the last codon to add an amino acid to the truncated protein, and this amino acid will be carried by the 5'-**CAA**-3' anticodon (codon-anticodon binding occurs in opposite



halting protein synthesis. Therefore, the codon just prior to the first stop codon will be the last codon to add an amino acid. In this case, (5'-UUG-3') is the last codon to add an amino acid to the truncated protein, and this amino acid will be carried by the 5'-CAA-3' anticodon (codon-anticodon binding occurs in opposite directions [ie, 5' to 3' binds 3' to 5']).

(Choice A) Because complementary sequences align in antiparallel fashion, during translation the tRNA anticodons will bind the 5' to 3' mRNA in the (opposite) 3' to 5' direction. Therefore, the 5'-UUG-3' mRNA codon will bind the 5'-CAA-3' tRNA anticodon, not the 5'-AAC-3' anticodon.

(Choices B and E) The 5'-AUC-3' and 5'-UCG-3' anticodons will bind to the 5'-GAU-3' and 5'-CGA-3' codons, respectively (5' to 3' binds 3' to 5'). These are not present in the above mRNA sequence.

(Choice D) The last codon shown in the above mRNA sequence is 5'-UAG-3' (a stop codon), with the second-to-last codon being 5'-AGC-3'. Therefore, 5'-GCU-3' would be the tRNA anticodon responsible for adding the last amino acid to the normal (non-truncated) protein.

Educational objective:

Translation of the mRNA template proceeds in the 5' to 3' direction. Because complementary sequences align in antiparallel fashion, during translation tRNA anticodons will be oriented in the opposite 3' to 5' direction. Stop codons (UAA, UAG, and UGA) halt protein synthesis by binding a release factor; they do

(Choice A) Because complementary sequences align in antiparallel fashion, during translation the tRNA anticodons will bind the 5' to 3' mRNA in the (opposite) 3' to 5' direction. Therefore, the 5'-UUG-3' mRNA codon will bind the 5'-CAA-3' tRNA anticodon, not the 5'-AAC-3' anticodon.

(Choices B and E) The 5'-AUC-3' and 5'-UCG-3' anticodons will bind to the 5'-GAU-3' and 5'-CGA-3' codons, respectively (5' to 3' binds 3' to 5'). These are not present in the above mRNA sequence.

(Choice D) The last codon shown in the above mRNA sequence is 5'-UAG-3' (a stop codon), with the second-to-last codon being 5'-AGC-3'. Therefore, 5'-GCU-3' would be the tRNA anticodon responsible for adding the last amino acid to the normal (non-truncated) protein.

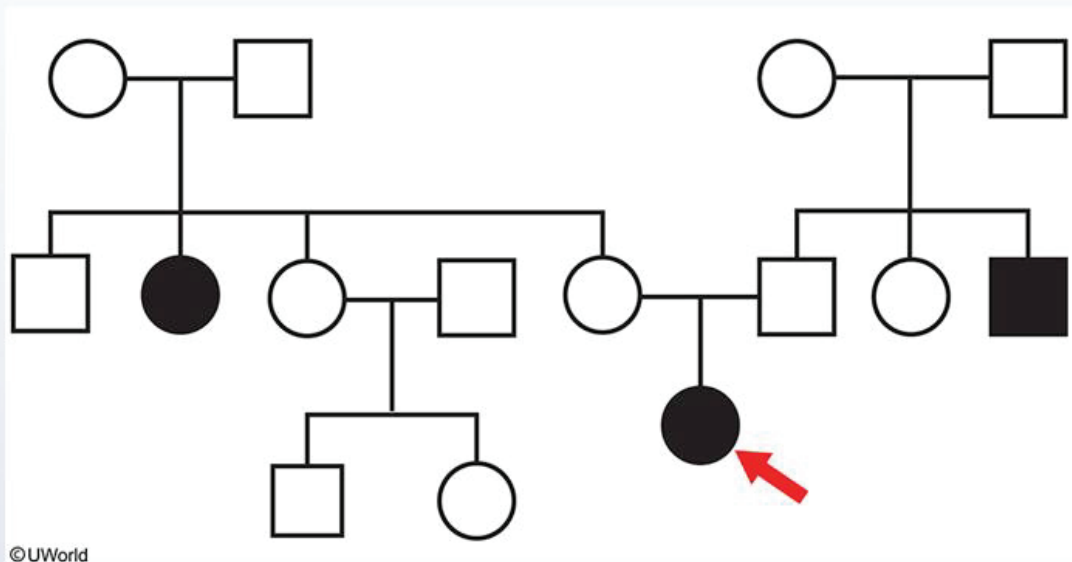
Educational objective:

Translation of the mRNA template proceeds in the 5' to 3' direction. Because complementary sequences align in antiparallel fashion, during translation tRNA anticodons will be oriented in the opposite 3' to 5' direction. Stop codons (UAA, UAG, and UGA) halt protein synthesis by binding a release factor; they do not add amino acids to the polypeptide chain.

Genetics	Genetics (General Principles)	Genetic code
Subject	System	Topic



A patient is suspected of having an inherited disorder. Pedigree analysis shows the following pattern:



This patient most likely has which of the following conditions?

- ☐ A. Classic galactosemia
- ☐ B. Hemophilia B





Previous

Next

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Lab Values

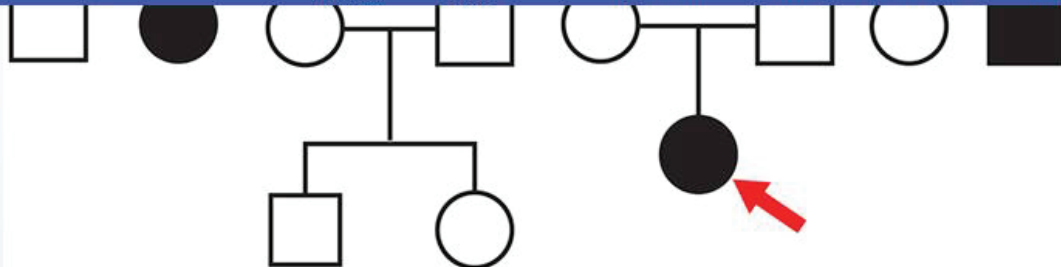
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This patient most likely has which of the following conditions?

- ☐ A. Classic galactosemia
- ☐ B. Hemophilia B
- ☐ C. Huntington disease
- ☐ D. Leber hereditary optic neuropathy
- ☐ E. Rett syndrome

Submit

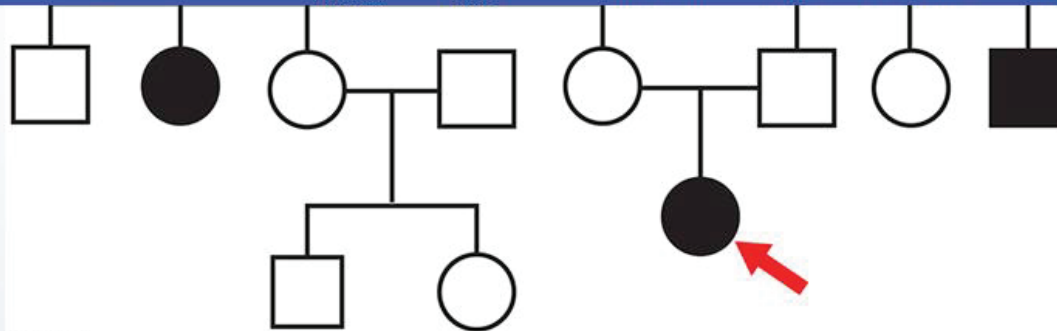
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This patient most likely has which of the following conditions?

- ☒ A. Classic galactosemia (64%)
- ☐ B. Hemophilia B (16%)
- ☐ C. Huntington disease (6%)
- ☐ D. Leber hereditary optic neuropathy (6%)
- ☐ E. Rett syndrome (6%)



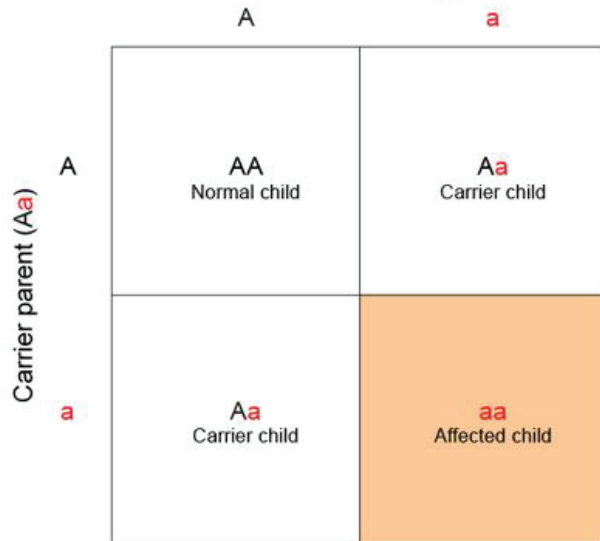


Autosomal recessive inheritance

Exhibit Display

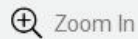
Autosomal recessive inheritance

Carrier parent (Aa)

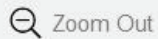


Offspring have 25% chance of being affected

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Offspring have 25% chance of being affected

Each of the affected individuals on this pedigree inherited the disorder from **asymptomatic carrier parents**, which is consistent with a recessive inheritance pattern. Because **both males and females** inherit the condition, it is an **autosomal recessive** disorder. Based on this inheritance pattern, 50% of offspring will be asymptomatic carriers, 25% will be unaffected, and 25% will express the disorder.

Classic galactosemia is the most common and most severe of the galactosemic disorders. It is an autosomal recessive disorder leading to complete enzymatic absence of galactose-1-phosphate uridyl transferase. Newborns present within days of birth with jaundice, vomiting, and hepatomegaly.

In general, most **enzyme deficiency conditions** follow an autosomal recessive inheritance pattern whereas diseases due to defective noncatalytic proteins follow an autosomal dominant pattern.

(Choice B) Hemophilia B (Christmas disease) is an **X-linked recessive disorder** affecting **males** that causes factor IX deficiency with easy bruising and bleeding (eg, hemarthrosis, oral bleeding, intracranial hemorrhage). Affected males will have asymptomatic carrier mothers.

(Choice C) Huntington disease is an **autosomal dominant disorder** affecting males and females equally. It causes progressive neurodegeneration of the caudate and putamen, leading to chorea, dementia, and



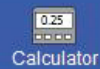
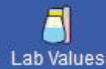
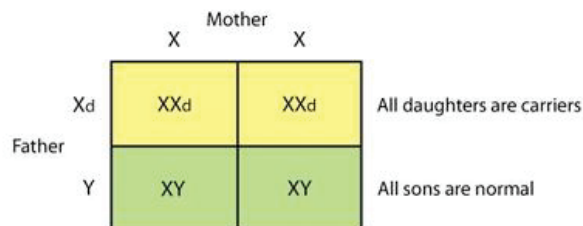


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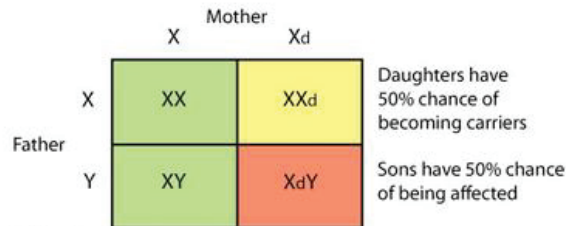
X-linked recessive inheritance Pedigrees- Stem

X-linked recessive inheritance

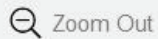
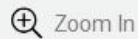
Affected father



Carrier mother



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(Choice C) Huntington disease is an **autosomal dominant disorder** affecting males and females equally. It causes progressive neurodegeneration of the caudate and putamen, leading to chorea, dementia, and death. Patients usually have an affected parent.

(Choice D) Leber hereditary optic neuropathy is a **mitochondrial inheritance disorder** affecting all offspring of an affected mother; there is no father-child transmission. It is characterized by progressive bilateral optic neuropathy leading to blindness.

(Choice E) Rett syndrome is an **X-linked dominant disorder** affecting females (affected males die in utero) that presents in early childhood with progressive neurodegeneration and stereotypical hand movements. X-linked dominant conditions are characterized by a lack of father-son transmission whereas all daughters of an affected father are affected. Half of all offspring of an affected mother are also affected.

Educational objective:

Autosomal recessive disorders affect 25% of offspring of asymptomatic heterozygous carrier parents.

Classical galactosemia is the most common and severe galactosemic disorder and presents within days of birth with jaundice, vomiting, and hepatomegaly.

Genetics Genetics (General Principles) Genetic inheritance

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Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

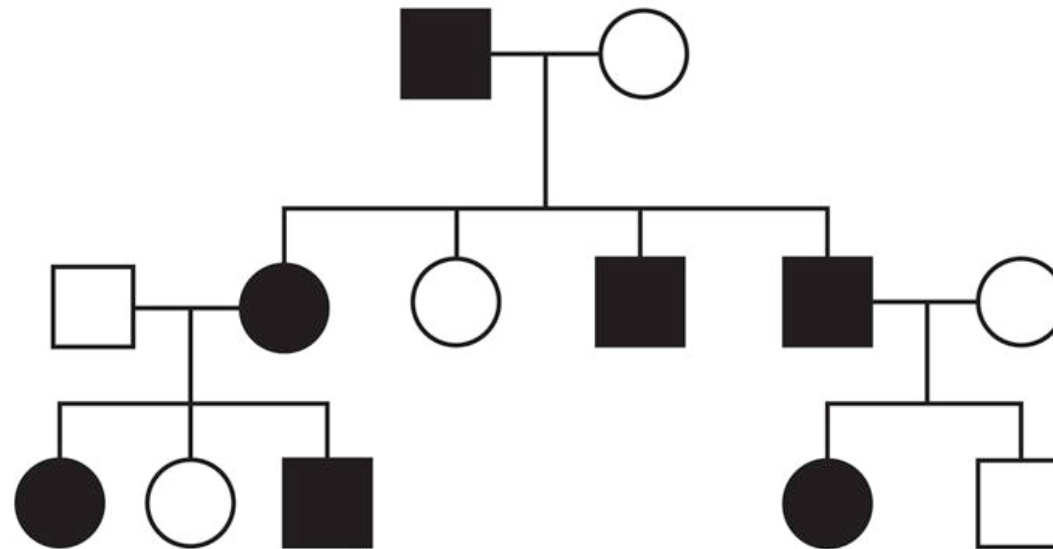
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Autosomal dominant disorder



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Genetics

Genetics (General Principles)

Genetic inheritance

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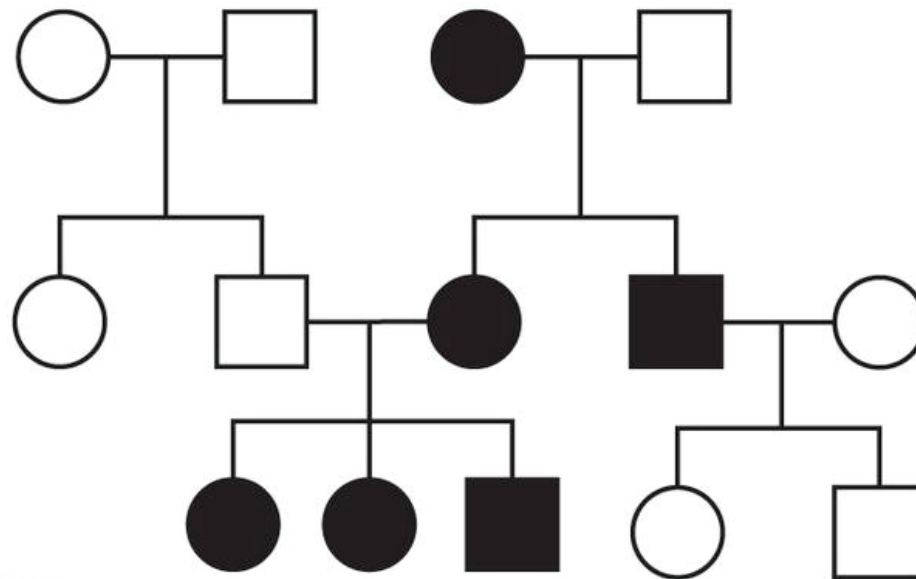
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Mitochondrial inheritance disorder



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Genetics Genetics (General Principles) Genetic inheritance

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Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

Exhibit Display

X-linked Dominant Inheritance Pedigrees- Stem

X-linked dominant inheritance

Affected father

	Mother		
	X		X
Father	X ^d	XX ^d	XX ^d
	Y	XY	XY

All daughters are affected

All sons are normal

Affected mother

	Mother		
	X		X ^d
Father	X	XX	XX ^d
	Y	XY	X ^d Y

All sons & daughters have 50% chance of being affected

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Genetics

Genetics (General Principles)

Genetic inheritance

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A 33-year-old woman, gravida 2 para 1, comes to the office for a prenatal visit at 20 weeks gestation. She feels well and reports experiencing fetal movements. The patient has no medical problems other than a history of cleft lip, which was repaired in childhood. Her husband is healthy, but her previous child was born with spina bifida. She takes a daily prenatal vitamin. Physical examination is unremarkable and uterine size is in accordance with ultrasound dates. The patient is worried that the fetus may develop the same birth defect as her previous child. Which of the following is the most likely mode of inheritance of this disorder?

- ☐ A. Autosomal dominant
- ☐ B. Autosomal recessive
- ☐ C. Mitochondrial
- ☐ D. Multifactorial
- ☐ E. X-linked recessive

Submit

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A 33-year-old woman, gravida 2 para 1, comes to the office for a prenatal visit at 20 weeks gestation. She feels well and reports experiencing fetal movements. The patient has no medical problems other than a history of cleft lip, which was repaired in childhood. Her husband is healthy, but her previous child was born with spina bifida. She takes a daily prenatal vitamin. Physical examination is unremarkable and uterine size is in accordance with ultrasound dates. The patient is worried that the fetus may develop the same birth defect as her previous child. Which of the following is the most likely mode of inheritance of this disorder?

- ☐ A. Autosomal dominant (5%)
- ☐ B. Autosomal recessive (5%)
- ☐ C. Mitochondrial (2%)
- ☒ D. Multifactorial (84%)
- ☐ E. X-linked recessive (1%)





Multifactorial inheritance is a term used to describe a complex process by which numerous genetic and environmental factors interact to determine phenotypic expression. Unlike single-gene disorders, diseases displaying multifactorial inheritance make precise genetic analysis and counseling extremely challenging due to their intricate development process. What is understood about these diseases is that the **closer a relative** is to the affected person, the **more likely** the relative is to develop the trait.

Spina bifida is an example of a multifactorial condition. There are a multitude of different genes that play a role in neurulation, the process responsible for formation of the neural tube. In addition to genetic factors, a number of environmental factors have profound effects on neural tube development; the most well known is dietary folate deficiency. Neural tube defects are more common in first-degree relatives of those affected, with a recurrence risk of 2%-5%. In general, most multifactorial conditions have a lower recurrence risk than autosomal dominant and autosomal recessive diseases, which convey a 50% and 25% risk to first-degree family members, respectively.

Other examples of multifactorial diseases include cleft lip and palate, diabetes mellitus, coronary artery disease, and hypertension.

(Choice A) A condition inherited in an *autosomal dominant* pattern will be expressed in 50% of offspring





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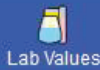
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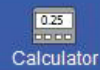
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Lab Values



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Calculator



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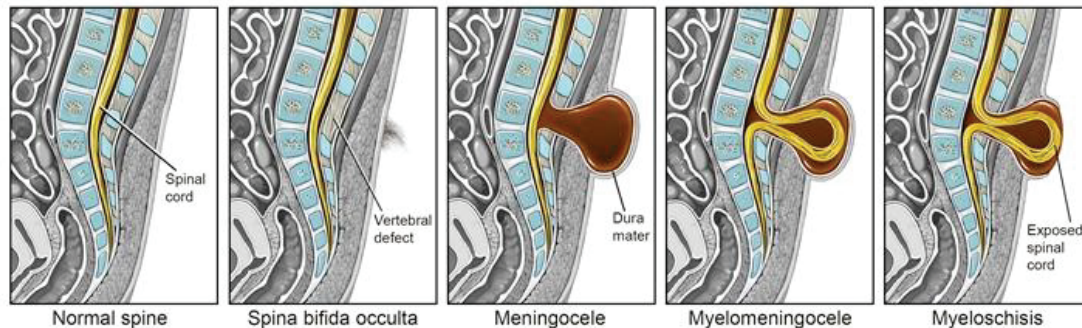
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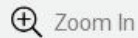
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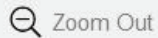
Spina bifida



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disease, and hypertension.

(Choice A) A condition inherited in an **autosomal dominant** pattern will be expressed in 50% of offspring when 1 parent is affected. Classic examples include Huntington disease, Marfan syndrome, multiple endocrine neoplasias, and the neurofibromatoses.

(Choice B) A condition inherited in an **autosomal recessive** fashion will be expressed in 25% of offspring when both parents are carriers. Cystic fibrosis, hemochromatosis, and sickle cell anemia are examples of autosomal recessive diseases.

(Choice C) Humans inherit mitochondrial DNA only from their mothers; therefore, mitochondrial inheritance is purely maternal. Disorders transmitted via mitochondrial inheritance display variable expressivity, meaning that severity of phenotypic expression can differ greatly even among close relatives. Examples of mitochondrial diseases are myoclonic epilepsy and Leber hereditary optic neuropathy.

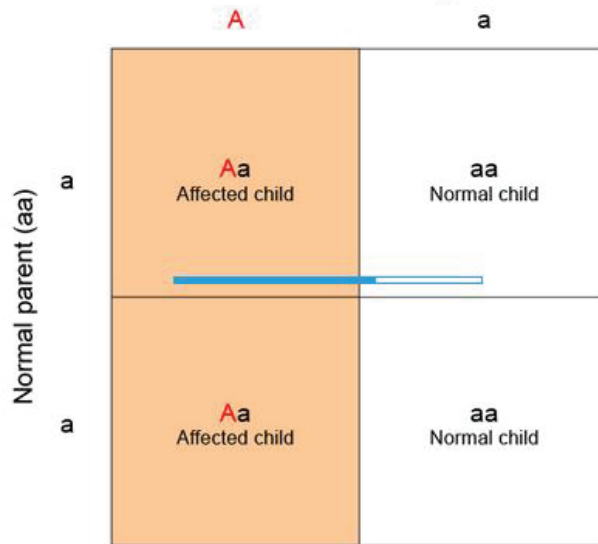
(Choice E) **X-linked recessive** inheritance refers to a trait that is passed via the X chromosome in a recessive manner. Phenotypic expression in offspring is dependent on the sex of the child; all males who inherit the X chromosome will display the phenotype whereas only homozygous females will display the phenotype. Examples include Duchenne and Becker muscular dystrophy, hemophilia, and G6PD deficiency.



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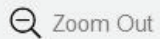
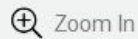
Autosomal dominant inheritance

Affected parent (Aa)



Offspring have 50% chance of being affected

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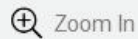
Autosomal recessive inheritance

Carrier parent (Aa)

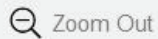
	A	a								
Carrier parent (Aa)	<table><tr><td>A</td><td>AA Normal child</td></tr><tr><td>a</td><td>Aa Carrier child</td></tr></table>	A	AA Normal child	a	Aa Carrier child	<table><tr><td>A</td><td>Aa Carrier child</td></tr><tr><td>a</td><td>aa Affected child</td></tr></table>	A	Aa Carrier child	a	aa Affected child
A	AA Normal child									
a	Aa Carrier child									
A	Aa Carrier child									
a	aa Affected child									

Offspring have 25% chance of being affected

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X-linked recessive inheritance

Affected father

		Mother			
		X		X	
Father	X ^d	XX ^d		XX ^d	All daughters are carriers
	Y	XY		XY	
					All sons are normal

Carrier mother

		Mother		
		X	X ^d	
Father	X	XX	XX ^d	Daughters have 50% chance of becoming carriers
	Y	XY	X ^d Y	

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(Choice C) Humans inherit mitochondrial DNA only from their mothers; therefore, mitochondrial inheritance is purely maternal. Disorders transmitted via mitochondrial inheritance display variable expressivity, meaning that severity of phenotypic expression can differ greatly even among close relatives. Examples of mitochondrial diseases are myoclonic epilepsy and Leber hereditary optic neuropathy.

(Choice E) **X-linked recessive** inheritance refers to a trait that is passed via the X chromosome in a recessive manner. Phenotypic expression in offspring is dependent on the sex of the child; all males who inherit the X chromosome will display the phenotype whereas only homozygous females will display the phenotype. Examples include Duchenne and Becker muscular dystrophy, hemophilia, and G6PD deficiency.

Educational objective:

Many frequently encountered diseases (eg, hypertension, spinal bifida) display multifactorial inheritance, which involves the complex interaction of numerous genetic and environmental factors to determine phenotypic expression. Although the exact inheritance risk cannot be determined, the closer a relative is to the affected person, the more likely the relative is to develop the trait.

References

- [Mouse as a model for multifactorial inheritance of neural tube defects.](#)





A 50-year-old previously healthy man is evaluated for progressive fatigue, weakness, and recurrent gingival bleeding. Laboratory studies reveal normocytic normochromic anemia, thrombocytopenia, and leukocytosis with circulating myeloblasts. Bone marrow biopsy establishes a diagnosis of acute myeloid leukemia. Induction chemotherapy followed by allogeneic hematopoietic cell transplantation (HCT) is planned. Molecular typing of human leukocyte antigen (HLA) -A, -B, -C, -DP, -DQ, and -DR is performed. The patient's biological sister, with whom he shares both parents, is eligible for stem cell donation and undergoes HLA typing. Which of the following is the most likely probability that the sibling will be an identical HLA match with this patient?

- ☐ A. 0
- ☐ B. 1/16
- ☒ C. 1/8
- ☐ D. 1/4
- ☐ E. 1/2





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Previous



Next



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Tutorial



Lab Values



Notes



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bleeding. Laboratory studies reveal normocytic normochromic anemia, thrombocytopenia, and leukocytosis with circulating myeloblasts. Bone marrow biopsy establishes a diagnosis of acute myeloid leukemia. Induction chemotherapy followed by allogeneic hematopoietic cell transplantation (HCT) is planned. Molecular typing of human leukocyte antigen (HLA) -A, -B, -C, -DP, -DQ, and -DR is performed. The patient's biological sister, with whom he shares both parents, is eligible for stem cell donation and undergoes HLA typing. Which of the following is the most likely probability that the sibling will be an identical **HLA match** with this patient?

- ☐ A. 0 (7%)
- ☐ B. 1/16 (15%)
- ☐ C. 1/8 (10%)
- ☒ D. 1/4 (55%)
- ☐ E. 1/2 (10%)

Correct

55%



51 secs



10/23/2020

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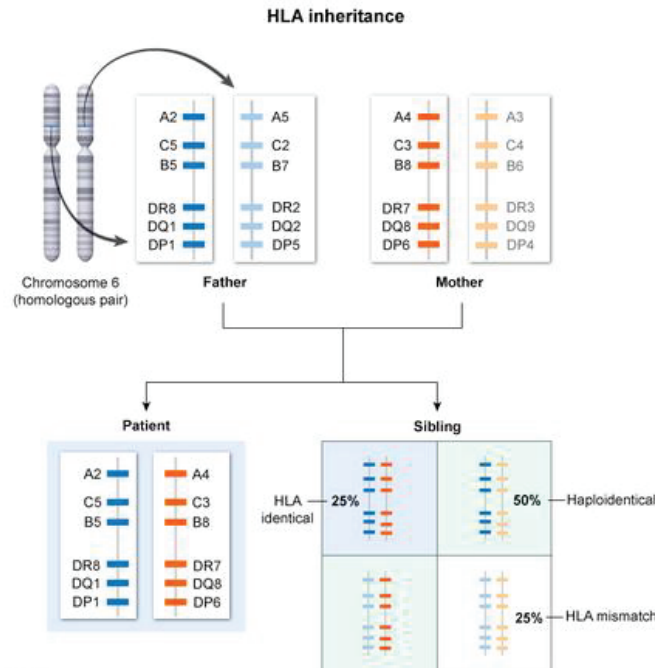
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The human leukocyte antigen (**HLA**) genes encode major histocompatibility complex (**MHC**) molecules that are expressed on the cell surface and are key to recognition of cells as **self or non-self** by the immune system. These include major class I genes (eg, HLA-A, HLA-B, HLA-C) and class II genes (eg, HLA-DP, HLA-DQ, HLA-DR), along with other minor HLA genes.

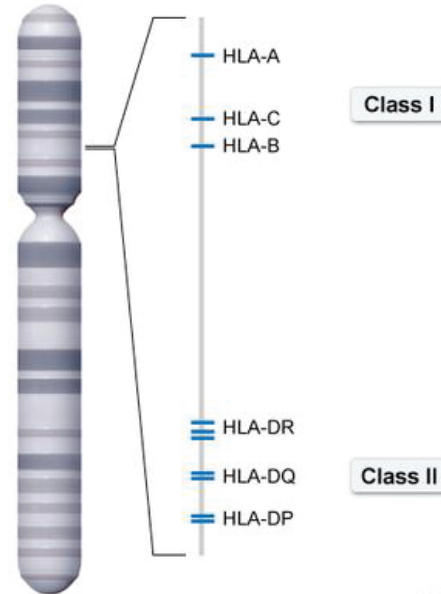
Although there are thousands of HLA alleles in the human population with millions of potential combinations, the HLA genes are **clustered** within a short region of a **single chromosome**. This results in a **low** rate of **crossover**, allowing the HLA gene cluster to be treated as an **HLA haplotype** (a series of **linked genes** on the same chromosome). Each child inherits 2 HLA haplotypes, one from the mother and one from the father. Therefore, the probabilities that a given sibling will share some or all of the same HLA genes are as follows:

- **1/4** chance of inheriting all the same HLA genes (ie, **identical HLA match**).
- **1/2** chance of inheriting half of the same HLA genes (ie, haploidentical HLA match) (**Choice E**).
- **1/4** chance of inheriting none of the same HLA genes (ie, HLA mismatch).

Molecular typing of HLA antigens is performed prior to transplants (eg, allogeneic stem cell transplant) to evaluate potential donors for mismatch in HLA alleles (eg, HLA-DR8 versus HLA-DR3), which is associated

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HLA genes (chromosome 6)



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- 1/4 chance of inheriting none of the same HLA genes (ie, HLA mismatch).

Molecular typing of HLA antigens is performed prior to transplants (eg, allogeneic stem cell transplant) to evaluate potential donors for mismatch in HLA alleles (eg, HLA-DR8 versus HLA-DR3), which is associated with higher rates of posttransplant complications (eg, graft versus host disease, graft failure). An **HLA-identical sibling donor** would drastically reduce the likelihood of serious complications and increase the likelihood of a **successful transplant**.

Educational objective:

The human leukocyte antigen (HLA) genes encode major histocompatibility complex (MHC) molecules that are key to activation of the immune system in response to foreign (non-self) antigens. All the HLA genes are clustered together, meaning that there is a low rate of crossover and that offspring essentially inherit 2 HLA haplotypes, one from each parent. Therefore, the probability that a sibling would be an identical HLA match is 1/4.

Genetics
Subject

Genetics (General Principles)
System

Genetic inheritance
Topic

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Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



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Text Zoom



Settings

A researcher develops 2 functional mRNA sequences composed of CUC and CUU trinucleotide repeats, respectively. He subsequently incubates these mRNAs in a solution containing functional ribosomes and tRNAs charged with the appropriate amino acids. After several hours, it is found that both mRNA sequences produce polypeptide chains containing leucine repeats. This observed finding is due to which of the following genetic principles?

- ☐ A. Ambiguity
- ☐ B. No punctuation
- ☐ C. Transition
- ☐ D. Universality
- ☐ E. Wobble

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Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



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Text Zoom




Settings

A researcher develops 2 functional mRNA sequences composed of CUC and CUU trinucleotide repeats, respectively. He subsequently incubates these mRNAs in a solution containing functional ribosomes and tRNAs charged with the appropriate amino acids. After several hours, it is found that both mRNA sequences produce polypeptide chains containing leucine repeats. This observed finding is due to which of the following genetic principles?

- ☐ A. Ambiguity (11%)
- ☐ B. No punctuation (0%)
- ☐ C. Transition (2%)
- ☐ D. Universality (7%)
- ☒ E. Wobble (78%)

Correct

 78%
Answered correctly 28 secs
Time Spent 02/14/2021
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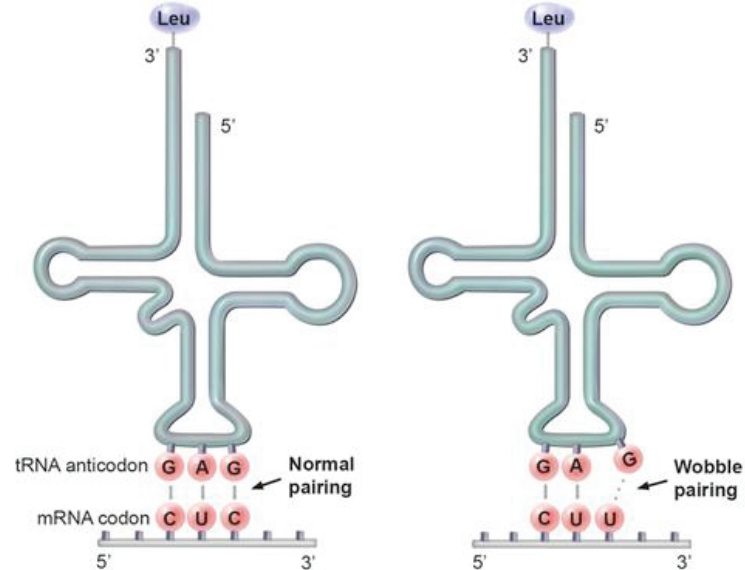
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Wobble hypothesis



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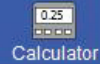
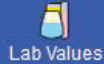
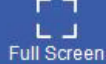
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There are 61 codons that code for amino acids, but only 20 amino acids are used in protein synthesis. The **genetic code** is therefore considered "**degenerate**" because more than 1 codon can code for a particular amino acid. For instance, the codons CUC and CUU both code for the amino acid leucine.

Individual tRNA molecules are specific for certain amino acids and recognize the mRNA codons associated with those amino acids. Certain tRNA molecules can recognize **multiple different codons** coding for the **same amino acid**, a phenomenon explained by the **wobble hypothesis**. This hypothesis states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base pairing with their complementary nucleotides on tRNA, whereas the third "wobble" nucleotide position may undergo less stringent (nontraditional) base pairing. In the case of leucine, for example, 1 tRNA molecule recognizes 2 codons (CUC and CUU) because only the first 2 nucleotide positions (CU in the codon) form traditional bonds.

(Choice A) The genetic code is not ambiguous as each codon is associated with only a single amino acid.

(Choice B) The genetic code is read sequentially from a starting point and has no internal punctuation as each codon is adjacent to the next without spacer nucleotides in between.

(Choice C) Genetic transition refers to a point mutation that results in replacement of a purine nucleotide

Block Time Remaining: 00:36:00

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Feedback

Suspend

End Block



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

each codon is adjacent to the next without spacer nucleotides in between.

(Choice C) Genetic transition refers to a point mutation that results in replacement of a purine nucleotide for another purine or a pyrimidine nucleotide for another pyrimidine. In contrast, transversion refers to a point mutation that results in the replacement of a purine nucleotide for a pyrimidine or a pyrimidine nucleotide for a purine.

(Choice D) The genetic code is almost universal as amino acid codons are nearly identical across species; however, mitochondria and some bacteria and single-celled eukaryotes deviate from the standard genetic code.

Educational objective:

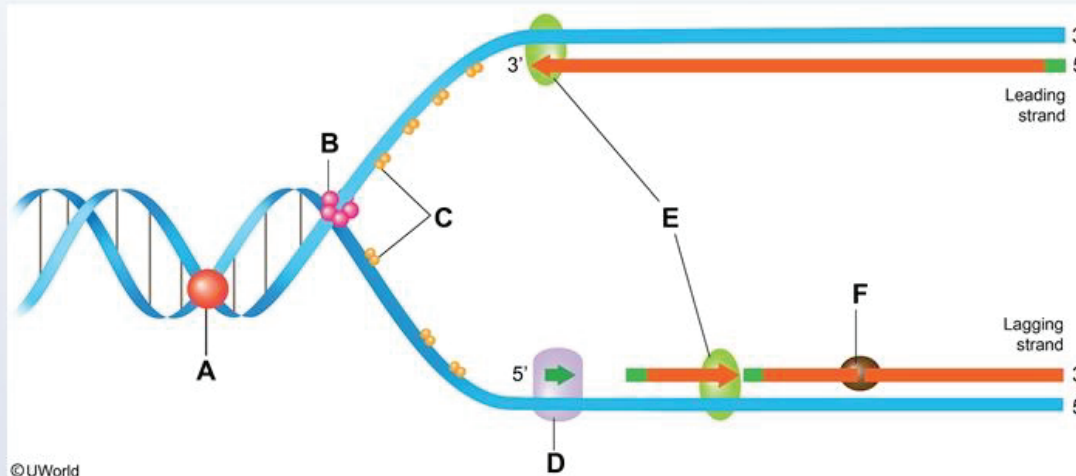
The genetic code is considered "degenerate" because more than 1 codon can code for a particular amino acid. Some of this degeneracy is explained by the wobble hypothesis, which states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base pairing, whereas the third "wobble" nucleotide position may undergo less stringent (nontraditional) base pairing.

References

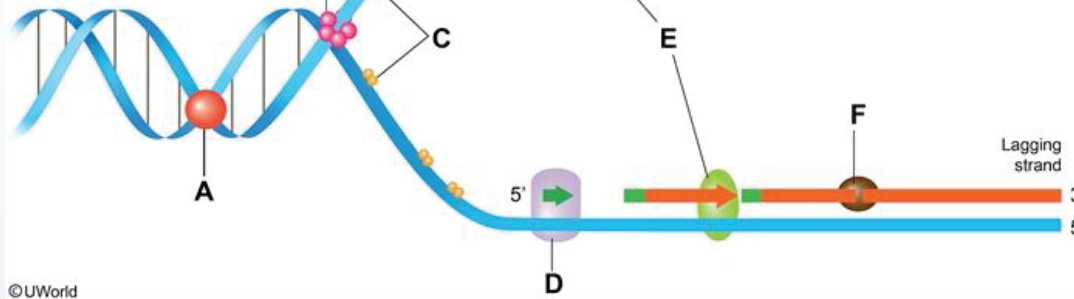
- tRNA's wobble decoding of the genome: 40 years of modification.



A 13-year-old boy with growth retardation, microcephaly, sun-sensitive skin rash, and recurrent infections is being evaluated for a possible inherited genetic defect. The patient is the second-born child of a first cousin marriage. His parents and siblings are healthy, but 2 of his maternal cousins have similar signs and symptoms. Genetic analysis of the patient reveals a defect in the *BLM* gene that codes for DNA helicase. Which of the following is the most likely site of action of this enzyme in the DNA replication fork shown below?



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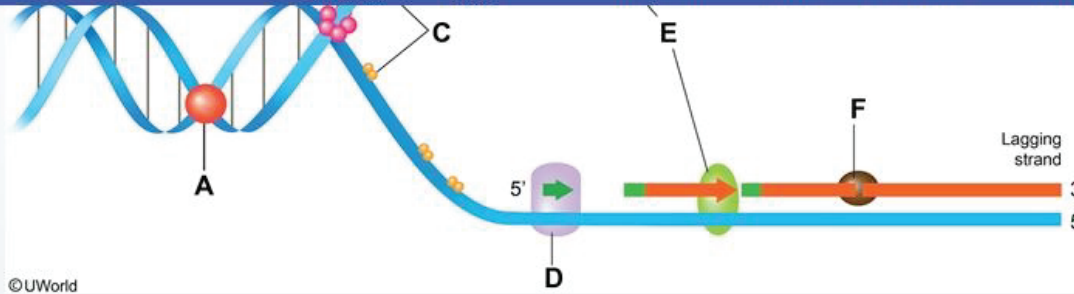
- ☐ A.A
- ☐ B.B
- ☐ C.C
- ☐ D.D
- ☐ E.E
- ☐ F.F

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- ☐ A.A (6%)
- ☒ B.B (86%)
- ☐ C.C (4%)
- ☐ D.D (0%)
- ☐ E.E (0%)
- ☐ F.F (0%)

Correct

86%

54 secs

01/12/2021

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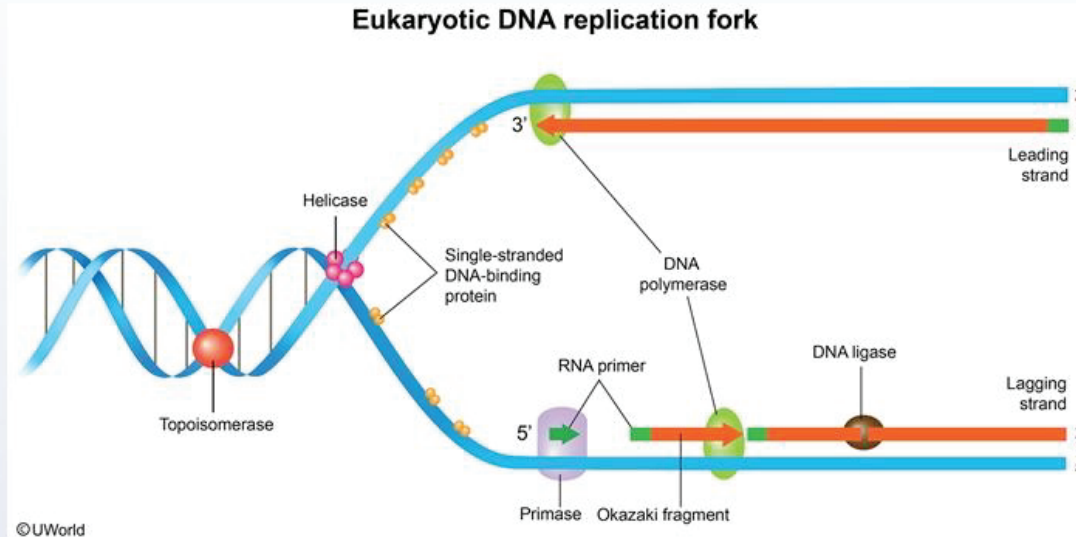
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This patient has **Bloom syndrome**, a rare autosomal recessive disorder caused by mutations in the *BLM* gene. This gene encodes DNA helicase, an enzyme responsible for unwinding of the double helix during DNA replication and repair. **Helicase dysfunction** results in chromosomal instability and breakage and manifests clinically with **growth retardation, facial anomalies** (eg, microcephaly), **photosensitive rash**, and **immunodeficiency** (eg, recurrent infections).



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

DNA replication occurs during the S phase (synthesis phase) of the cell cycle and is coordinated by the effects of multiple proteins. First, the origin of replication is identified and bound by a multi-subunit protein (the origin recognition complex), which locally dissociates double-stranded DNA (dsDNA) into single-stranded DNA (ssDNA). ssDNA-binding proteins then bind to and stabilize the ssDNA, preventing it from reannealing **(Choice C)**.

Helicase subsequently binds to ssDNA at the origin of replication, moves into the replication fork, and proceeds to separate and unwind the dsDNA. As DNA is unwound, superhelical tension is generated as supercoils are being formed. Topoisomerase relieves this tension by introducing transient single- or double-stranded nicks in the DNA. This enzyme is located ahead of helicase on the dsDNA segment of the replication fork **(Choice A)**.

(Choice D) Before DNA polymerase can begin synthesizing DNA, it requires an RNA primer made up of short RNA sequences base-paired to the parent DNA. This primer is synthesized by the enzyme primase (DNA-dependent RNA polymerase).

(Choice E) DNA polymerase synthesizes new daughter strand DNA in the 5' to 3' direction. The leading strand is formed continuously, whereas the lagging strand is formed discontinuously, creating Okazaki fragments.



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Feedback



Suspend



End Block



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

short RNA sequences base-paired to the parent DNA. This primer is synthesized by the enzyme primase (DNA-dependent RNA polymerase).

(Choice E) DNA polymerase synthesizes new daughter strand DNA in the 5' to 3' direction. The leading strand is formed continuously, whereas the lagging strand is formed discontinuously, creating Okazaki fragments.

(Choice F) Okazaki fragments are ultimately bound together by the enzyme ligase.

Educational objective:

Bloom syndrome is a rare autosomal recessive condition caused by mutations in the *BLM* gene encoding helicase, an enzyme that unwinds the double helix during DNA replication. Patients typically present with growth retardation, facial anomalies, photosensitive skin rash, and immunodeficiency due to chromosomal instability and breakage.

References

- Clinical features of Bloom syndrome and function of the causative gene, BLM helicase.
- The replication fork: understanding the eukaryotic replication machinery and the challenges to genome duplication.



0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

A 23-year-old previously healthy man comes to the office after noticing a painless, hard mass in the left testis. Scrotal ultrasound shows a solid testicular mass, and CT scan of the abdomen and pelvis shows left paraaortic lymphadenopathy. Left orchidectomy is performed and postoperative histopathology reveals seminoma of the testis. External beam radiotherapy is administered to the paraaortic metastatic area. Several weeks later, the retroperitoneal nodes are observed to have markedly decreased in size. Which of the following is the most likely effect of the therapy used on the metastatic cells in this patient?

- ☐ A. Demethylation of DNA
- ☐ B. DNA cross-linking
- ☐ C. Double-strand DNA breaks
- ☐ D. Nucleotide mismatches
- ☐ E. Pyrimidine dimers

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0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

A 23-year-old previously healthy man comes to the office after noticing a **painless, hard mass** in the left testis. Scrotal ultrasound shows a solid testicular mass, and CT scan of the abdomen and pelvis shows left paraaortic lymphadenopathy. Left orchidectomy is performed and postoperative histopathology reveals **seminoma** of the testis. External beam radiotherapy is administered to the paraaortic metastatic area. Several weeks later, the retroperitoneal nodes are observed to have markedly decreased in size. Which of the following is the most likely effect of the therapy used on the metastatic cells in this patient?

- ☐ A. Demethylation of DNA (4%)
- ☐ B. DNA cross-linking (10%)
- ☒ C. Double-strand DNA breaks (64%)
- ☐ D. Nucleotide mismatches (2%)
- ☐ E. Pyrimidine dimers (17%)

Correct

64%
Answered correctly
55 secs
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12/11/2020
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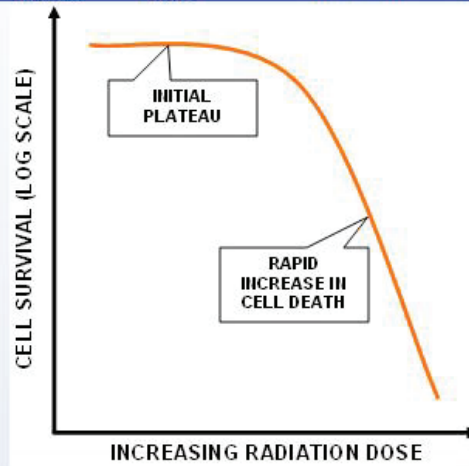
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Therapeutic **ionizing radiation** (eg, gamma rays, x-rays), commonly used to treat or palliate several types of cancer, can cause cell death through 2 major mechanisms:

- **DNA double-strand breakage:** Breakage of both strands is generally required, as single strand breaks are readily repaired by polymerases.
- **Free radical formation:** Reactive oxygen species are formed by ionization of water; oxygen free radicals are then able to cause cellular and DNA damage.

The effect of radiation is most pronounced in malignant cells as they are rapidly dividing and consequently



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

The effect of radiation is most pronounced in malignant cells as they are rapidly dividing and consequently less able to repair DNA damage. Epithelial surfaces (eg, bowel mucosa, skin) are also severely affected because they are rapidly dividing.

A characteristic cell death curve of exposure to radiation shows a nearly flat line on initial exposure, followed by a steep increase in cell death as the radiation dose increases (Diagram). The steep portion is due to a sharp increase in double-stranded DNA strand fractures and oxygen free radicals.

(Choice A) DNA methylation (only cytosine and adenine) typically inhibits gene transcription.

Demethylation or hypomethylation of oncogenes (and hypermethylation of tumor suppressor genes) contributes to the development of some cancers.

(Choice B) DNA cross-linking can be induced by numerous chemical and physical agents, notably alkylating agents used in cancer treatment.

(Choice D) During DNA replication, incorrect base placement can occur, but enzymes scan the newly synthesized DNA strands for mismatched bases, which are then excised and replaced. This process is guided by the presence of adenine methylation (recognized by the enzymes) in the template strand, as the daughter strand remains unmethylated for some time following DNA replication.

(Choice E) DNA damage from exposure to ultraviolet radiation, a non-ionizing radiation, leads to the





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

(Choice B) DNA cross-linking can be induced by numerous chemical and physical agents, notably alkylating agents used in cancer treatment.

(Choice D) During DNA replication, incorrect base placement can occur, but enzymes scan the newly synthesized DNA strands for mismatched bases, which are then excised and replaced. This process is guided by the presence of adenine methylation (recognized by the enzymes) in the template strand, as the daughter strand remains unmethylated for some time following DNA replication.

(Choice E) DNA damage from exposure to ultraviolet radiation, a non-ionizing radiation, leads to the formation of pyrimidine-pyrimidine dimers (thymine dimers). Ionizing radiation has higher energy (enough to remove an electron), leading to more cell damage.

Educational objective:

Exposure to ionizing radiation, including therapeutic and palliative radiation therapy, induces DNA damage through DNA double-strand fractures and the formation of oxygen free radicals.

Genetics

Genetics (General Principles)

Radiation injury

Subject

System

Topic

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A researcher is studying the Fas receptor (FasR), a protein widely expressed on cell surfaces. The signaling cascade of programmed cell death is initiated when FasR binds to its ligand (FasL), which is expressed on cytotoxic T cells. In an experiment, cancer cells that escaped elimination by the immune system were found to contain soluble Fas proteins that did not promote apoptosis. The soluble Fas proteins were shorter and lacked the transmembrane domain. DNA analysis of these cells revealed no *FAS* gene mutations. Which of the following is the most likely explanation for the formation of altered Fas proteins in these cancer cells?

- ☐ A. Alternative splicing
- ☐ B. Defective polyadenylation
- ☐ C. DNA methylation
- ☐ D. Polycistronic mRNA
- ☐ E. Protein ubiquitination

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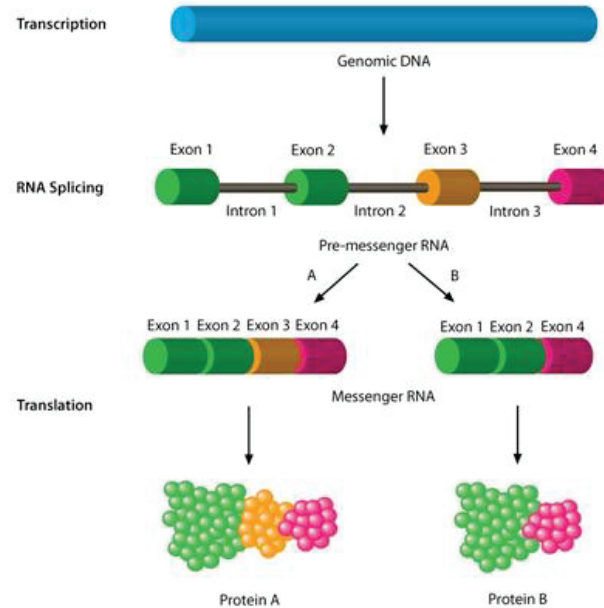


A researcher is studying the Fas receptor (FasR), a protein widely expressed on cell surfaces. The signaling cascade of programmed cell death is initiated when FasR binds to its ligand (FasL), which is expressed on cytotoxic T cells. In an experiment, cancer cells that escaped elimination by the immune system were found to contain soluble Fas proteins that did not promote apoptosis. The soluble Fas proteins were shorter and lacked the transmembrane domain. DNA analysis of these cells revealed no FAS gene mutations. Which of the following is the most likely explanation for the formation of altered Fas proteins in these cancer cells?

- ☒ A. Alternative splicing (70%)
- ☐ B. Defective polyadenylation (7%)
- ☐ C. DNA methylation (11%)
- ☐ D. Polycistronic mRNA (3%)
- ☐ E. Protein ubiquitination (8%)



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Alternative splicing is a process by which different combinations of DNA coding regions (**exons**) are selectively included or excluded from a mature messenger RNA (mRNA) transcript. This allows the DNA contained in a single gene to code for a functionally diverse group of proteins.

Splicing is a post-transcriptional modification that removes noncoding DNA regions (**introns**) from precursor-mRNA (pre-mRNA). The process is driven by a large protein complex (**spliceosome**) comprised of small nuclear ribonucleoproteins (snRNPs). Pre-mRNA splice sites are bound by the spliceosome, forming a lariat-shaped intermediate containing the introns. This intermediate is excised and the exons are joined, completing the splicing process.

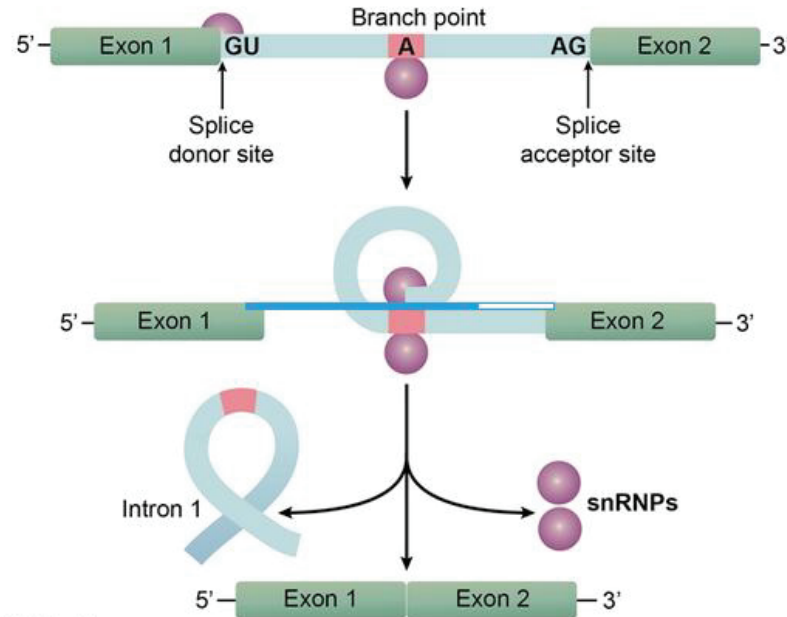
Alternative splicing is a normal process that allows production of alternate sets of proteins in different tissues. It has also been implicated in various human diseases. Cancers in particular can use alternative splicing to evade innate defense mechanisms. The **Fas receptor-Fas ligand** interaction drives programmed cell death via the cytotoxic T-cell mediated extrinsic pathway. Cancer cells may develop the ability to **splice out** a particular exon that codes for the **transmembrane domain** of the Fas receptor (FasR), converting it to a soluble form that is not expressed on the cell surface, which allows the cells to **evade apoptosis**.

(Choice B) Polyadenylation is a post-transcriptional modification in which a tail comprised of multiple



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Splicing of pre-mRNA



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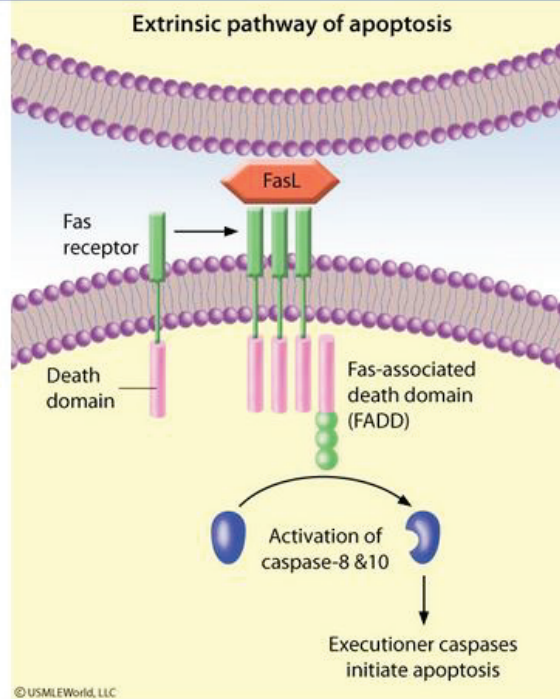
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Extrinsic pathway of apoptosis



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(Choice B) Polyadenylation is a post-transcriptional modification in which a tail comprised of multiple adenosine nucleotides is added to the 3' end of a new mRNA transcript. This process is necessary for the nuclear export and cytoplasmic stability of mRNA.

(Choice C) DNA methylation describes the process by which methyl groups are added to DNA, suppressing transcription of the methylated genes.

(Choice D) Polycistronic mRNA is often found in bacteria and contains multiple open reading frames that are translated into several proteins. In contrast, eukaryotic organisms have monocistronic mRNA, which codes for only one protein.

(Choice E) Ubiquitination is a process by which certain proteins are tagged with ubiquitin, a small regulatory protein, marking them for proteasomal degradation.

Educational objective:

Alternative splicing is a process by which a single gene can code for various unique proteins by selectively including or excluding different DNA coding regions (exons) into mature mRNA.

References

- [Alternative pre-mRNA splicing regulation in cancer.](#)





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

Electron microscopy of a eukaryotic cell during interphase of the cell cycle shows 10-nm thick chromatin fibers with a "beads on a string" appearance. These chromatin fibers are extracted and treated with an endonuclease, which preferentially cleaves the "string" portions of the chromatin. Further evaluation of the "beads" reveals that they are composed of DNA wrapped around a core of proteins. Which of the following proteins is most likely found outside of this core and helps promote chromatin compaction?

- ☐ A. Histone H1
- ☐ B. Histone H3
- ☐ C. Histone H4
- ☐ D. snRNP
- ☐ E. Topoisomerase II
- ☐ F. Ubiquitin

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Mark



Previous



Next



Full Screen



Tutorial



Lab Values



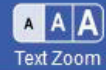
Notes



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Reverse Color



Text Zoom



Settings

Electron microscopy of a **eukaryotic** cell during **interphase** of the cell cycle shows 10-nm thick chromatin fibers with a "beads on a string" appearance. These chromatin fibers are extracted and treated with an endonuclease, which preferentially cleaves the "string" portions of the chromatin. Further evaluation of the "beads" reveals that they are composed of DNA wrapped around a core of proteins. Which of the following proteins is most likely found **outside** of this core and helps promote chromatin compaction?

- ☒ A. Histone H1 (73%)
- ☐ B. Histone H3 (6%)
- ☐ C. Histone H4 (11%)
- ☐ D. snRNP (2%)
- ☐ E. Topoisomerase II (3%)
- ☐ F. Ubiquitin (2%)

Correct



73%

Answered correctly



44 secs

Time Spent



02/28/2021

Last Updated

Block Time Remaining: 00:41:19

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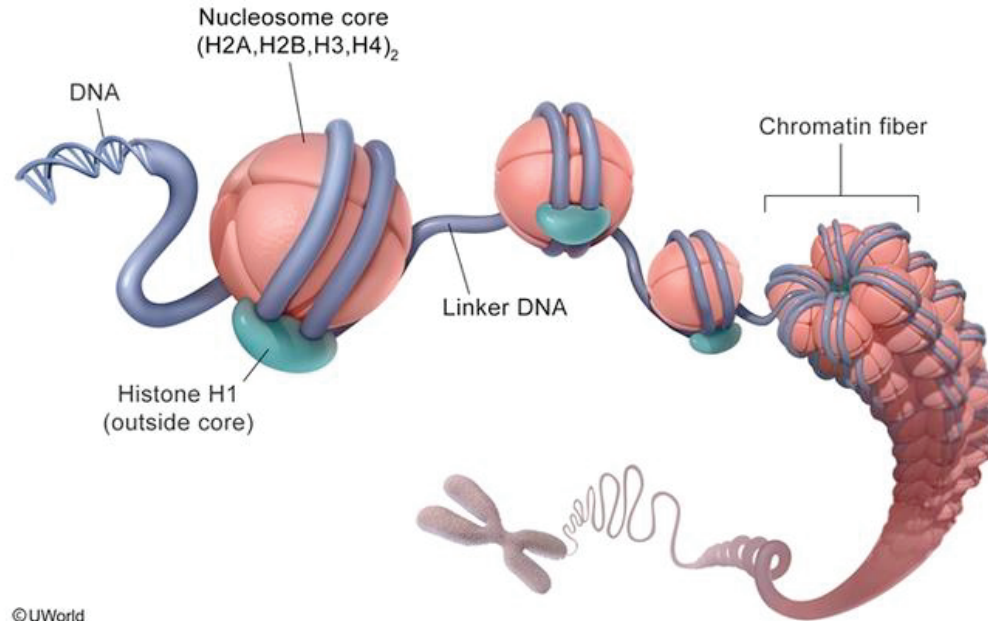
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End Block

Exhibit Display

Eukaryotic DNA organization



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Zoom Out

Reset

New | Existing

My Notebook



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

Nucleosomes are structural subunits within the nucleus of eukaryotic cells that are composed of DNA wrapped around a core of histone proteins. There are 5 major subtypes of histones: H1, H2A, H2B, H3, and H4. Each histone core is made up of 8 histone proteins: 2 molecules each of H2A, H2B, H3, and H4 (**Choices B and C**). During the initial steps of DNA packaging into chromatin, the negatively charged DNA double helix wraps around the positively charged histone core twice.

In contrast to the other histone proteins, **H1** is located **outside** of the **histone core**. H1 histones bind the **linker** segments of DNA that lie between nucleosomes and facilitate **packaging of nucleosomes** into more compact structures. DNA associated with histones has the appearance of "beads on a string." This structure undergoes further rounds of coiling and associates with other proteins (eg, nuclear scaffold protein), ultimately forming chromosomes.

(Choice D) Small nuclear ribonucleoproteins (snRNPs) help to splice out introns from pre-mRNA, forming mature mRNA.

(Choice E) During prokaryotic DNA replication, topoisomerase II (DNA gyrase) relieves the tension created during DNA strand unwinding by introducing negative supercoils into the DNA.

(Choice F) Ubiquitin is a small protein present in the cytoplasm and nucleus of all eukaryotes. It is typically covalently attached to various intracellular proteins to signal for their degradation by the



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Feedback



Suspend



End Block



structure undergoes further rounds of coiling and associates with other proteins (eg, nuclear scaffold protein), ultimately forming chromosomes.

(Choice D) Small nuclear ribonucleoproteins (snRNPs) help to splice out introns from pre-mRNA, forming mature mRNA.

(Choice E) During prokaryotic DNA replication, topoisomerase II (DNA gyrase) relieves the tension created during DNA strand unwinding by introducing negative supercoils into the DNA.

(Choice F) Ubiquitin is a small protein present in the cytoplasm and nucleus of all eukaryotes. It is typically covalently attached to various intracellular proteins to signal for their degradation by the proteasome (ubiquitin-proteasome pathway).

Educational objective:

Nucleosomes are composed of DNA wrapped around a core of 8 histone proteins (2 molecules each of H2A, H2B, H3, and H4). H1 histone is located outside of this histone core and helps package nucleosomes into more compact structures by binding and linking the DNA between adjacent nucleosomes.

References

- [H1 histones: current perspectives and challenges.](#)





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

A 65-year-old woman with chronic obstructive pulmonary disease and type II diabetes mellitus comes to the emergency department due to profound fevers and malaise. After initial evaluation, she is hospitalized for septicemia. Blood cultures plated on lactose-containing media grow rapidly dividing gram-negative bacteria. Replication of these microbial cells requires synthesis of two daughter strands of DNA using the parent strands as templates. Which of the following processes will differ the most between the 2 daughter strands formed at each replication fork?

- ☐ A. Enzymatic function of DNA helicase
- ☐ B. Interaction with single-stranded DNA-binding proteins
- ☐ C. Joining of DNA fragments by ligase
- ☐ D. Proofreading of the newly synthesized DNA
- ☐ E. Relief of supercoils by topoisomerase

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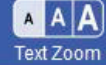
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End Block



A 65-year-old woman with chronic obstructive pulmonary disease and type II diabetes mellitus comes to the emergency department due to profound fevers and malaise. After initial evaluation, she is hospitalized for septicemia. Blood cultures plated on lactose-containing media grow rapidly dividing gram-negative bacteria. Replication of these microbial cells requires synthesis of two daughter strands of DNA using the parent strands as templates. Which of the following processes will differ the most between the 2 daughter strands formed at each replication fork?

- ☐ A. Enzymatic function of DNA helicase (2%)
- ☐ B. Interaction with single-stranded DNA-binding proteins (8%)
- ☒ C. Joining of DNA fragments by ligase (65%)
- ☐ D. Proofreading of the newly synthesized DNA (19%)
- ☐ E. Relief of supercoils by topoisomerase (3%)

Correct

 65%
Answered correctly 01 min, 07 secs
Time Spent 02/08/2021
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Block Time Remaining: 00:42:26

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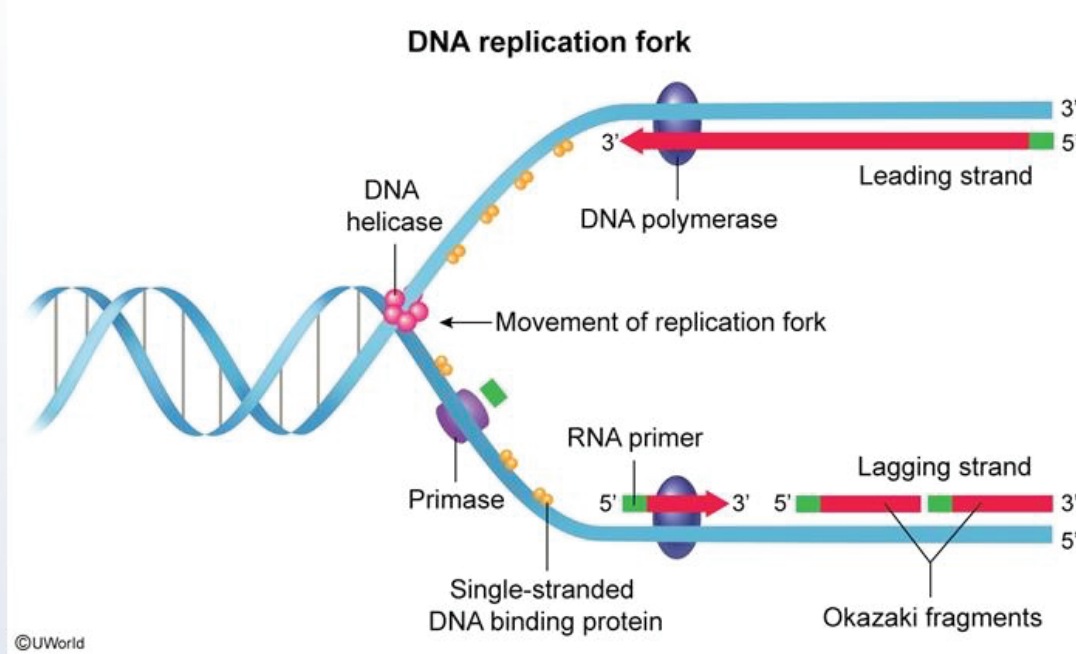
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End Block



DNA replication is similar in prokaryotes and eukaryotes, with DNA polymerases I and III being the main polymerase enzymes involved in prokaryotic DNA replication. For DNA replication to begin, DNA helicase must first unwind the DNA double helix and separate the parent strands (**Choice A**). The unwound single-stranded DNA is stabilized by the binding of single-stranded DNA binding proteins to prevent spontaneous



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

polymerase enzymes involved in prokaryotic DNA replication. For DNA replication to begin, DNA helicase must first unwind the DNA double helix and separate the parent strands (**Choice A**). The unwound single-stranded DNA is stabilized by the binding of single-stranded DNA-binding proteins to prevent spontaneous reannealing (**Choice B**).

Synthesis of the daughter strands occurs simultaneously from both parent strands. Because **DNA synthesis can occur only in the 5'→3' direction**, one daughter strand is synthesized continuously toward the replication fork (leading strand). However, the other strand must be synthesized **discontinuously** in a direction away from the replication fork (lagging strand), with more and more segments being added as the replication fork moves across the DNA double helix. This results in the formation of **Okazaki fragments**, short stretches of newly synthesized DNA that are separated by RNA primers. These primers are removed and replaced with DNA, and the Okazaki fragments are subsequently joined together by DNA ligase. Because of the discontinuous nature of DNA synthesis on the lagging strand, **DNA ligase** acts many more times on the lagging strand than on the leading strand.

(**Choice D**) DNA polymerases I and III have proofreading ability (ie, 3'→5' exonuclease activity), and the proofreading function of these polymerases is not restricted to either the leading or lagging strand.

(**Choice E**) Topoisomerase II produces negative supercoiling in the DNA helix ahead of the replication fork



0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

and replaced with DNA, and the Okazaki fragments are subsequently joined together by DNA ligase.

Because of the discontinuous nature of DNA synthesis on the lagging strand, **DNA ligase** acts many more times on the lagging strand than on the leading strand.

(Choice D) DNA polymerases I and III have proofreading ability (ie, 3'→5' exonuclease activity), and the proofreading function of these polymerases is not restricted to either the leading or lagging strand.

(Choice E) Topoisomerase II produces negative supercoiling in the DNA helix ahead of the replication fork to reduce the strain produced by unwinding, which causes positive supercoiling.

Educational objective:

DNA replication occurs in the 5'→3' direction on both strands. In contrast to the continuous synthesis of the leading strand, lagging strand synthesis occurs discontinuously and is composed of short stretches of RNA primer plus newly synthesized DNA segments (Okazaki fragments). As a result, lagging strand synthesis requires the repetitive action of DNA primase and DNA ligase.

References

- [Timing, coordination, and rhythm: acrobatics at the DNA replication fork.](#)

Genetics

Genetics (General Principles)

Dna replication

Block Time Remaining: 00:42:26

<https://t.me/USMLEWorldStep1>

0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

An 18-year-old man comes to the office due to abnormal skin pigmentation and premature hair graying. His nails are also thin and break easily, and he has white patches on his tongue. The patient's father had similar features at a young age and died of progressive pulmonary fibrosis. Physical examination shows diffuse gray hair, areas of reticular hyperpigmentation on the torso, dystrophic nails, and oral leukoplakia. Genetic testing reveals a loss-of-function mutation affecting the telomerase reverse transcriptase gene. Which of the following cell types is likely to be most affected by this mutation?

- ☐ A. Cardiac myocytes
- ☐ B. CNS neurons
- ☐ C. Compact bone osteocytes
- ☐ D. Hematopoietic stem cells
- ☐ E. Vascular endothelial cells

Submit

Block Time Remaining: 00:42:28

<https://t.me/USMLEWorldStep1>

0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

An 18-year-old man comes to the office due to abnormal skin pigmentation and premature hair graying. His nails are also thin and break easily, and he has white patches on his tongue. The patient's father had similar features at a young age and died of progressive pulmonary fibrosis. Physical examination shows diffuse gray hair, areas of reticular hyperpigmentation on the torso, dystrophic nails, and oral leukoplakia. Genetic testing reveals a loss-of-function mutation affecting the telomerase reverse transcriptase gene. Which of the following cell types is likely to be most affected by this mutation?

- ☐ A. Cardiac myocytes (1%)
- ☐ B. CNS neurons (5%)
- ☐ C. Compact bone osteocytes (2%)
- ☒ D. Hematopoietic stem cells (79%)
- ☐ E. Vascular endothelial cells (10%)

Correct

 79%
Answered correctly 58 secs
Time Spent 02/07/2021
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Block Time Remaining: 00:43:24

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Feedback

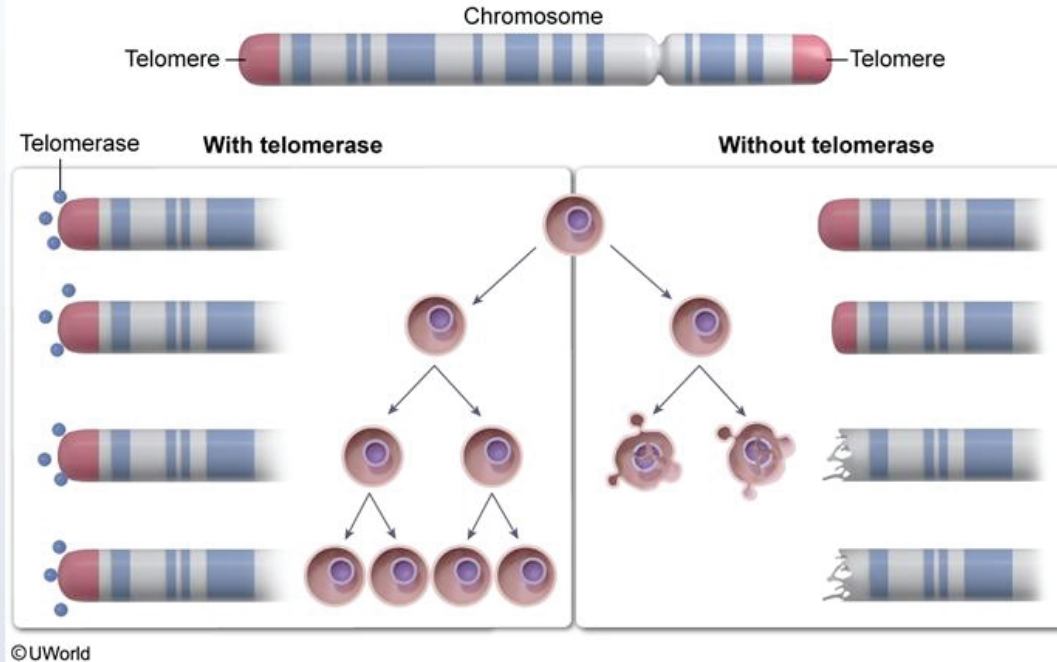


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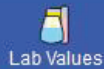


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Effect of telomerase on cell division



This patient has dyskeratosis congenita; a genetic disorder involving a mutation in the genes related to



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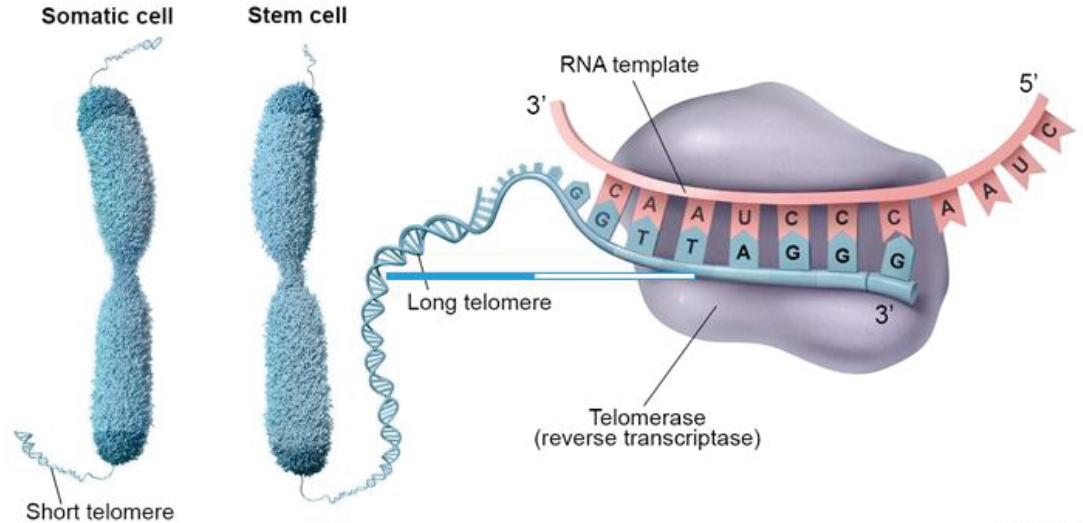
This patient has dyskeratosis congenita; a genetic disorder involving a mutation in the genes related to telomere maintenance (eg, telomerase reverse transcriptase) that results in short telomeres. **Telomeres** are a complex of protein (eg, shelterin) and DNA repeats (eg, TTAGGG) at the ends of chromosomes that **prevent chromosomal degradation** and fusion with neighboring chromosomes. With each cellular division telomeres progressively shorten, eventually reaching a critical length at which apoptosis or senescence is triggered.

In cells with a high turnover rate (eg, epithelial cells, lymphocytes, **hematopoietic stem cells**), telomere length is maintained by **telomerase**. This complex, composed of an RNA template and a reverse transcriptase, adds DNA repeats to the end of telomeres as they are lost with cell division. Without normal telomerase activity, rapidly dividing cells cannot maintain chromosomal integrity, triggering **premature cell death**. In patients with short telomere disorders, loss of these cells can cause characteristic mucocutaneous changes (eg, oral leukoplakia, dystrophic nails), **bone marrow failure** (eg, pancytopenia), and pulmonary fibrosis (due to alveolar epithelial dysfunction).

(Choices A, B, C, and E) Telomerase is inactivated in long-lived, differentiated cells such as cardiac myocytes, CNS neurons, compact bone osteocytes, and vascular endothelial cells; therefore, these cells



Exhibit Display





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

transcriptase, adds DNA repeats to the end of telomeres as they are lost with cell division. Without normal telomerase activity, rapidly dividing cells cannot maintain chromosomal integrity, triggering **premature cell death**. In patients with short telomere disorders, loss of these cells can cause characteristic mucocutaneous changes (eg, oral leukoplakia, dystrophic nails), **bone marrow failure** (eg, pancytopenia), and pulmonary fibrosis (due to alveolar epithelial dysfunction).

(Choices A, B, C, and E) Telomerase is inactivated in long-lived, differentiated cells such as cardiac myocytes, CNS neurons, compact bone osteocytes, and vascular endothelial cells; therefore, these cells are not likely to be affected by this patient's mutation. However, in cancer cells derived from differentiated cells, telomerase is reactivated, allowing continuous cellular division without loss of telomere length.

Educational objective:

Telomeres help maintain chromosomal integrity and are preserved in rapidly dividing cell lines (eg, epithelial cells, lymphocytes, hematopoietic stem cells) by telomerase. Disorders involving telomerase function (eg, dyskeratosis congenita) result in premature death of cells with high turnover, characteristically causing mucocutaneous changes (eg, oral leukoplakia, dystrophic nails), bone marrow failure, and pulmonary fibrosis.

References

- [Bone marrow failure and the telomeropathies.](#)



Feedback

Suspend

End Block

A genetic study performed on a 10-year-old boy reveals a single base substitution mutation involving a DNA segment that encodes a cellular protein, as shown in the image below.

Normal coding strand: 5' --- GCCCAATCT --- TATAAA --- CAAGCTCGTCATGCGGAG --- 3'

Patient's coding strand: 5' --- GCCCAATCT --- TAGAAA --- CAAGCTCGTCATGCGGAG --- 3'

-75 bp -25 bp +1 bp (Transcription start site)

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This mutation is most likely to affect which of the following processes?

- ☐ A. DNA methylation
- ☐ B. Polypeptide folding following translation
- ☐ C. Posttranscriptional RNA splicing
- ☐ D. RNA elongation
- ☐ E. Transcription initiation
- ☐ F. Translation initiation



Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

DNA segment that encodes a **cellular protein**, as shown in the image below.

Normal coding strand: 5'---GCCCAATCT---TATAAA---CAAGCTCGTCATGCGGAG---3'

Patient's coding strand: 5'---GCCCAATCT---TAGAAA---CAAGCTCGTCATGCGGAG---3'

-75 bp -25 bp +1 bp (Transcription start site)

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This mutation is most likely to affect which of the following processes?

- ☐ A. DNA methylation (2%)
- ☐ B. Polypeptide folding following translation (3%)
- ☐ C. Posttranscriptional RNA splicing (4%)
- ☐ D. RNA elongation (2%)
- ☒ E. Transcription initiation (82%)
- ☐ F. Translation initiation (4%)

Correct

82%

52 secs

01/25/2021

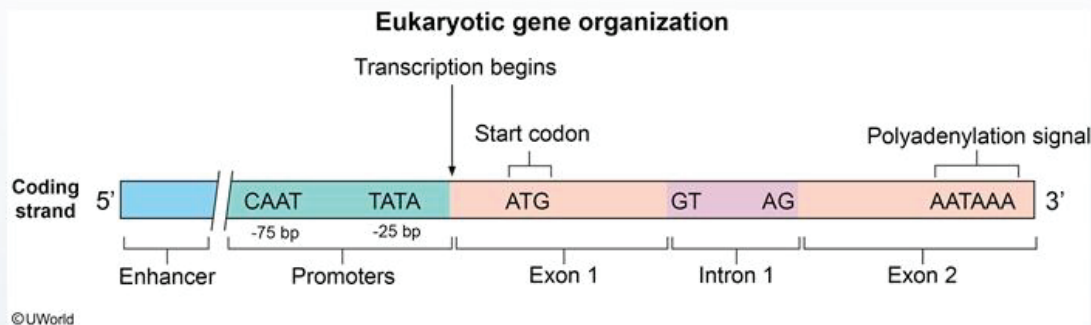
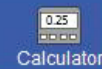
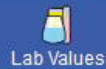
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Feedback

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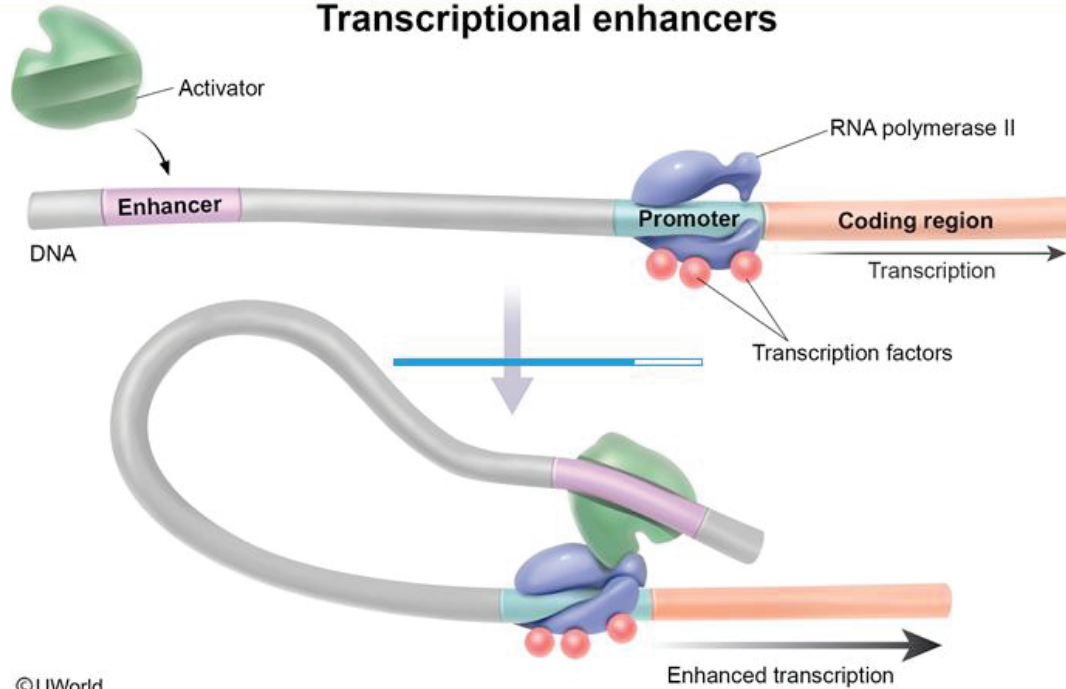
Genetic information flows from DNA to RNA to proteins. Most eukaryotic DNA sequences consist of coding exons, noncoding introns, and 2 **promoter regions** (the CAAT box and the TATA box). The CAAT box is located 70-80 bases upstream of the beginning (5' end) of the coding region, and the **TATA box** is located **25 bases upstream** from the beginning of the coding region.

Gene transcription begins when **RNA polymerase II** attaches to one of the promoter regions in a process that requires general **transcription factors**. A DNA **enhancer region** then binds activator proteins that associate with transcription factors and RNA polymerase II at the promoter, thereby increasing gene expression. Although promoters are not directly translated into protein, promoter mutations can cause abnormal gene expression by altering the ability of RNA polymerase II and transcription factors to bind.



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Transcriptional enhancers



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Zoom Out

Reset

New | Existing

My Notebook



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

(Choice A) DNA methylation is part of the epigenetic code. This process is carried out by DNA methyltransferases and serves to silence the genes it affects.

(Choice B) The folding of a formed polypeptide into its secondary and tertiary structures is entirely spontaneous and is determined by the amino acid sequence in the protein's primary structure. Heat shock proteins assist in the spontaneous refolding of proteins.

(Choice C) Posttranscriptional RNA splicing is facilitated by small nuclear ribonucleoproteins (snRNPs) that remove introns from heterogeneous nuclear RNA (hnRNA) containing GU at the 5' splice site and AG at the 3' splice site.

(Choice D) The TATA box only participates in the initiation of transcription. The addition of nucleotides to the forming RNA molecule (RNA elongation) continues until RNA polymerase II encounters a termination signal.

(Choice F) In eukaryotes, translation initiation requires both ribosomal subunits (60S and 40S) with their associated rRNA, mRNA, initiation factors, initiator tRNA charged with methionine, and GTP. The assembled ribosome then recognizes the AUG start codon on mRNA to begin the process.

Educational objective:

Block Time Remaining: 00:44:16

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0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

(Choice C) Posttranscriptional RNA splicing is facilitated by small nuclear ribonucleoproteins (snRNPs) that remove introns from heterogeneous nuclear RNA (hnRNA) containing GU at the 5' splice site and AG at the 3' splice site.

(Choice D) The TATA box only participates in the initiation of transcription. The addition of nucleotides to the forming RNA molecule (RNA elongation) continues until RNA polymerase II encounters a termination signal.

(Choice F) In eukaryotes, translation initiation requires both ribosomal subunits (60S and 40S) with their associated rRNA, mRNA, initiation factors, initiator tRNA charged with methionine, and GTP. The assembled ribosome then recognizes the AUG start codon on mRNA to begin the process.

Educational objective:

The TATA box is a promoter region that binds transcription factors and RNA polymerase II during the initiation of transcription. It is located approximately 25 bases upstream from the beginning of the coding region.

References

- RNA polymerase II transcription initiation: a structural view.



0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color

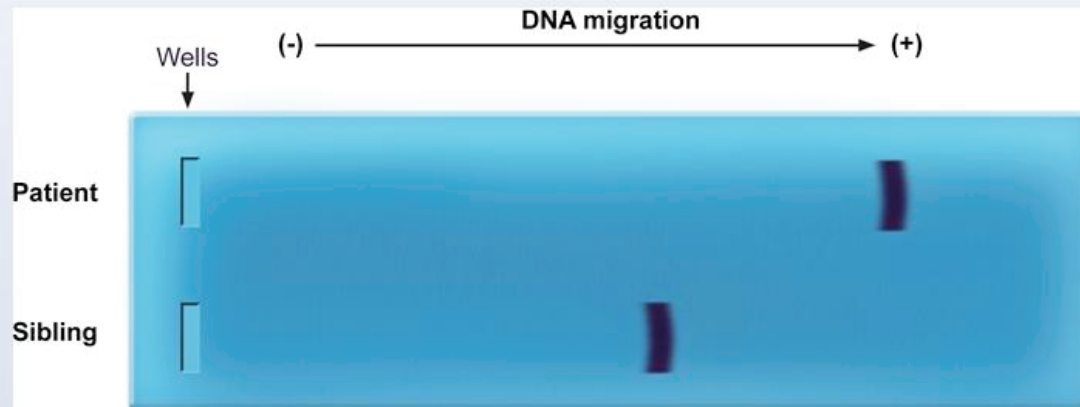


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Settings

A 3-year-old boy is being evaluated for recurrent respiratory infections. The patient's family immigrated to the United States 5 months after his birth. Since then, the boy has experienced multiple episodes of pneumonia and bronchitis, and has developed a persistent cough and failure to thrive. His older brother has no medical issues. A genetic test is performed and reveals a mutation in an exon of a gene that codes for a transmembrane chloride channel. The abnormal mRNA is isolated from cultured epithelial cells, and its complementary DNA is synthesized. Amplified cDNA samples from both the patient and his healthy sibling are analyzed using gel electrophoresis and compared to DNA fragments of known size to determine base pair length. The results are shown below.



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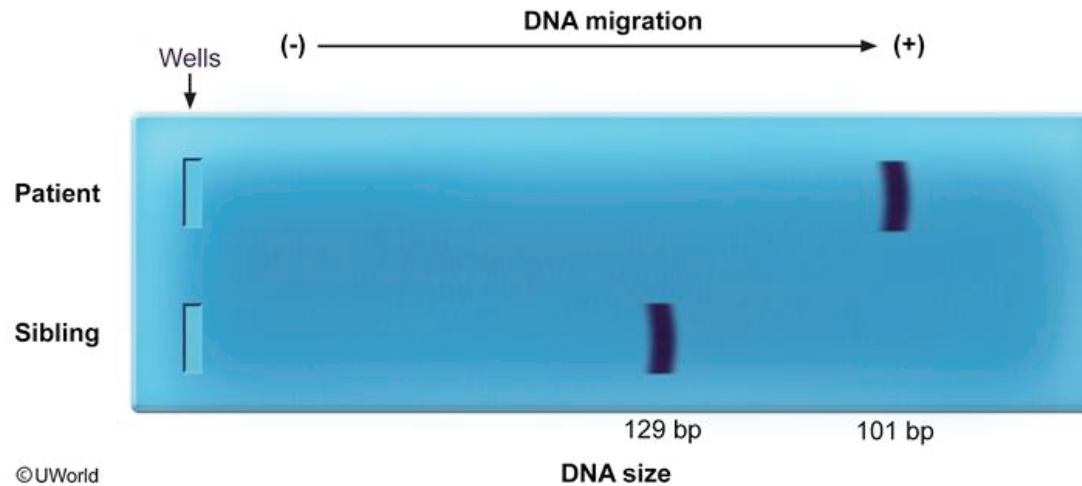


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Exhibit Display





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color

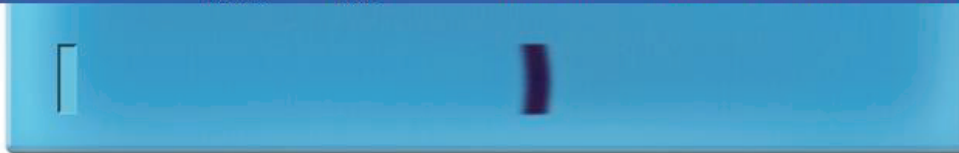


Text Zoom



Settings

Sibling



129 bp

101 bp

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DNA size

Which of the following is most likely responsible for this patient's condition?

- ☐ A. Frameshift mutation
- ☐ B. In-frame deletion
- ☐ C. Missense mutation
- ☐ D. Nonsense mutation
- ☐ E. Silent mutation
- ☐ F. Trinucleotide expansion

Submit

Block Time Remaining: 00:44:26

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0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color

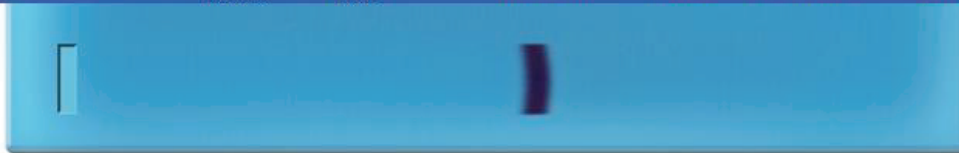


Text Zoom



Settings

Sibling



129 bp

101 bp

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DNA size

Which of the following is most likely responsible for this patient's condition?

- ☒ A. Frameshift mutation (24%)
- ☐ B. In-frame deletion (15%)
- ☐ C. Missense mutation (10%)
- ☐ D. Nonsense mutation (47%)
- ☐ E. Silent mutation (0%)
- ☐ F. Trinucleotide expansion (1%)

Correct



24%

Answered correctly



01 min, 17 secs

Time spent



03/08/2021

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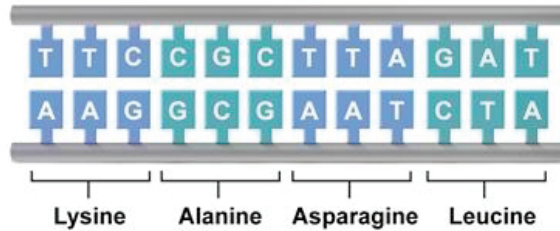
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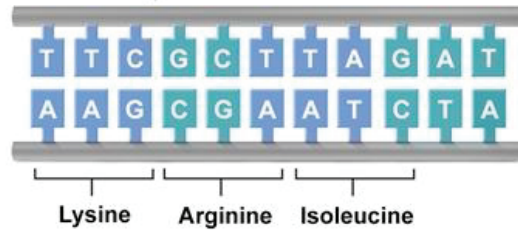
End Block

Exhibit Display

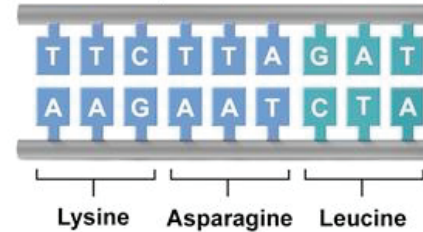
Normal



Frame shift deletion



In-frame deletion



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Zoom Out

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New | Existing

My Notebook



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

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This patient has cystic fibrosis, which occurs due to mutations affecting the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The vignette states that the patient's **mutation affects an exon**, meaning that the mutation will be **detectable in the mRNA** sequence. Complementary DNA (cDNA) is double-stranded DNA that is synthesized from an mRNA template. In this case, cDNA was synthesized using *CFTR* mRNA from the patient and his brother. Subsequent gel electrophoresis shows that the patient's cDNA is 28 base pairs shorter than that of his brother, indicating the patient has a **28-base pair deletion** affecting the coding region of *CFTR*. Deletion or insertion of a number of bases that is **not divisible by 3** results in **frameshift mutations**. As the name implies, frameshift mutations alter the reading frame of the genetic code, resulting in the formation of nonfunctional proteins due to the incorporation of many incorrect amino acids.

(Choice B) One or more complete codons (genetic triplet codes) are removed in an in-frame deletion, which does not affect the reading frame of subsequent codons. This patient's 28-base pair deletion is not divisible by 3, so it will result in a reading frame shift.

(Choices C and D) Missense and nonsense mutations are due to single base substitutions that result in the placement of an incorrect amino acid or introduction of a premature stop codon, respectively. These mutations occur in exons and affect protein translation. However, in this scenario, **gel electrophoresis** is

Block Time Remaining: 00:45:35

<https://t.me/USMLEWorldStep1>

0



Feedback



Suspend



End Block



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

(Choices C and D) Missense and nonsense mutations are due to single base substitutions that result in the placement of an incorrect amino acid or introduction of a premature stop codon, respectively. These mutations occur in exons and affect protein translation. However, in this scenario, **gel electrophoresis** is being performed on **cDNA (not protein)** and the results indicate the **length of the mature RNA transcript**. Termination of RNA transcription occurs by specific sequences in the 3' untranslated region that cause RNA hairpin loop formation and/or recruitment of termination factors. As a result, point mutations in the exons of a gene (such as those responsible for causing nonsense mutations) are unlikely to affect total mRNA (cDNA) size.

(Choice E) Silent mutations can occur in both coding and noncoding regions, but they do not alter protein quantity or function and do not affect phenotype. This patient's mutation caused him to develop cystic fibrosis, so it is not a silent mutation.

(Choice F) Trinucleotide expansions increase the number of trinucleotide repeats in the coding region of a gene, often resulting in large proteins with abnormal function. This patient's abnormal *CFTR* gene is shorter (not longer) than the normal gene from his sibling, which indicates a deletion has occurred.

Educational objective:

Deletion or addition of a number of bases that is not divisible by 3 in the coding region of a gene will cause





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

transcript. Termination of RNA transcription occurs by specific sequences in the 3' untranslated region that cause RNA hairpin loop formation and/or recruitment of termination factors. As a result, point mutations in the exons of a gene (such as those responsible for causing nonsense mutations) are unlikely to affect total mRNA (cDNA) size.

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(Choice F) Trinucleotide expansions increase the number of trinucleotide repeats in the coding region of a gene, often resulting in large proteins with abnormal function. This patient's abnormal *CFTR* gene is shorter (not longer) than the normal gene from his sibling, which indicates a deletion has occurred.

Educational objective:

Deletion or addition of a number of bases that is not divisible by 3 in the coding region of a gene will cause a frameshift mutation. Frameshift mutations alter the reading frame of the genetic code, resulting in the formation of nonfunctional proteins.

References

- The *CFTR* frameshift mutation 3905insT and its effect at transcript and protein level.



0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



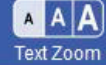
Notes



Calculator



Reverse Color



Text Zoom



Settings

A research scientist purifies DNA polymerase III from *Escherichia coli* extract. When the enzyme is incubated in a mixture containing DNA templates, RNA primer oligonucleotides, and tagged deoxynucleotides, she finds that the enzyme possesses 3' to 5' exonuclease activity. Which of the following enzymatic actions was most likely observed during the experiment?

- ☐ A. Cleavage of DNA strands to remove supercoils
- ☐ B. Excision of thymine dimers within DNA
- ☒ C. Removal of mismatched base pairs during DNA replication
- ☐ D. Removal of RNA primer nucleotides
- ☐ E. Unwinding of the 2 strands of template DNA

Submit

0



Feedback



Suspend



End Block



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom




Settings

A research scientist purifies DNA polymerase III from *Escherichia coli* extract. When the enzyme is incubated in a mixture containing DNA templates, RNA primer oligonucleotides, and tagged deoxynucleotides, she finds that the enzyme possesses 3' to 5' exonuclease activity. Which of the following enzymatic actions was most likely observed during the experiment?

- ☐ A. Cleavage of DNA strands to remove supercoils (1%)
- ☐ B. Excision of thymine dimers within DNA (4%)
- ☒ C. Removal of mismatched base pairs during DNA replication (70%)
- ☐ D. Removal of RNA primer nucleotides (21%)
- ☐ E. Unwinding of the 2 strands of template DNA (2%)

Correct

 70%
Answered correctly 03 mins, 06 secs
Time Spent 01/12/2021
Last Updated

Explanation

Block Time Remaining: 00:48:42

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Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

Proteins & their function in prokaryotic DNA replication

Helicase	Unwinding of double helix
Topoisomerase II (DNA gyrase)	Removal of supercoils
Single-stranded DNA-binding protein	Stabilization of unwound template strands
Primase (RNA polymerase)	Synthesis of RNA primer
DNA polymerase III	5' to 3' DNA synthesis & 3' to 5' exonuclease ("proofreading") activity
DNA polymerase I	Same as DNA polymerase III Also removes RNA primer (5' to 3' exonuclease activity) & replaces it with DNA
DNA ligase	Joining of Okazaki fragments (lagging strand)

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Block Time Remaining: 00:48:42

<https://t.me/USMLEWorldStep1>

0



Feedback



Suspend



End Block



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Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

DNA replication is coordinated by the actions of multiple enzymes and proteins and requires a high degree of fidelity to ensure preservation of the genetic code in daughter cells.

DNA polymerases are the primary enzymes responsible for DNA synthesis. Prokaryotes such as *Escherichia coli* have 3 major types of DNA polymerase: I, II, and III. All 3 **prokaryotic DNA polymerases** are capable of removing mismatched nucleotides via their **3' to 5' exonuclease ("proofreading") activity**. Only **DNA polymerase I** has **5' to 3' exonuclease activity**, which is used to remove the RNA primer synthesized by RNA primase (**Choice D**).

(Choice A) In prokaryotes, topoisomerase II (DNA gyrase) temporarily cleaves both strands of the DNA double helix and introduces negative supercoils into the circular DNA to relieve tension created during strand unwinding.

(Choice B) One of the major methods of DNA damage by ultraviolet (UV) light is the dimerization of adjacent pyrimidine bases to form thymidine dimers. These dimers are routinely formed after exposure to sunlight but are usually removed via nucleotide excision repair by the enzyme UV-specific endonuclease.

(Choice E) Helicase promotes unwinding and dissociation of parent DNA strands at the replication fork.

Educational objective:

Block Time Remaining: 00:48:42

<https://t.me/USMLEWorldStep1>



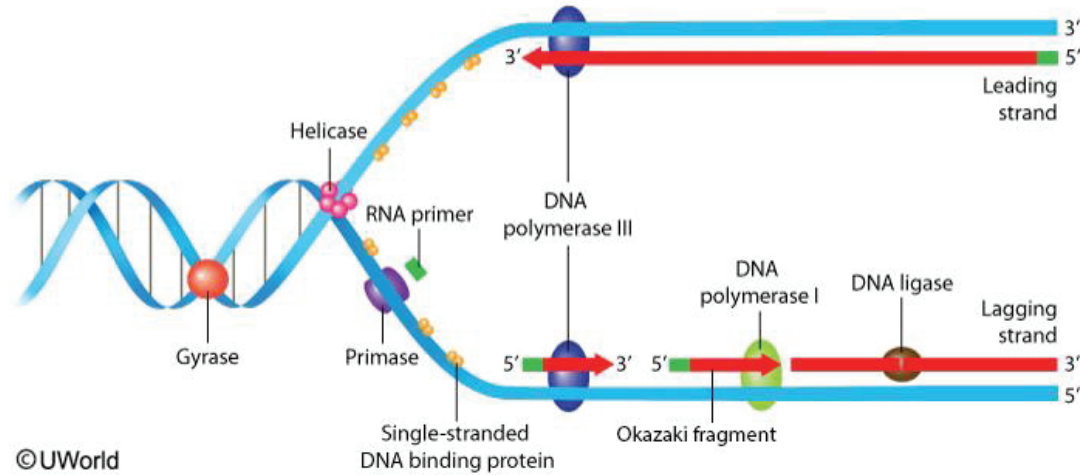
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Suspend

End Block

Exhibit Display

Prokaryotic DNA replication fork



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Block Time Remaining: 00:48:42

<https://t.me/USMLEWorldStep1>





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

(Choice A) In prokaryotes, topoisomerase II (DNA gyrase) temporarily cleaves both strands of the DNA double helix and introduces negative supercoils into the circular DNA to relieve tension created during strand unwinding.

(Choice B) One of the major methods of DNA damage by ultraviolet (UV) light is the dimerization of adjacent pyrimidine bases to form thymidine dimers. These dimers are routinely formed after exposure to sunlight but are usually removed via nucleotide excision repair by the enzyme UV-specific endonuclease.

(Choice E) Helicase promotes unwinding and dissociation of parent DNA strands at the replication fork.

Educational objective:

All 3 prokaryotic DNA polymerases can remove mismatched nucleotides via their 3' to 5' exonuclease ("proofreading") activity. Only DNA polymerase I has 5' to 3' exonuclease activity, which is used to remove the RNA primer synthesized by RNA primase.

References

- [DNA replication fidelity in Escherichia coli: a multi-DNA polymerase affair.](#)

Genetics

Genetics (General Principles)

Dna replication

Subject

System

Topic

Block Time Remaining: 00:48:42

<https://t.me/USMLEWorldStep1>

Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color

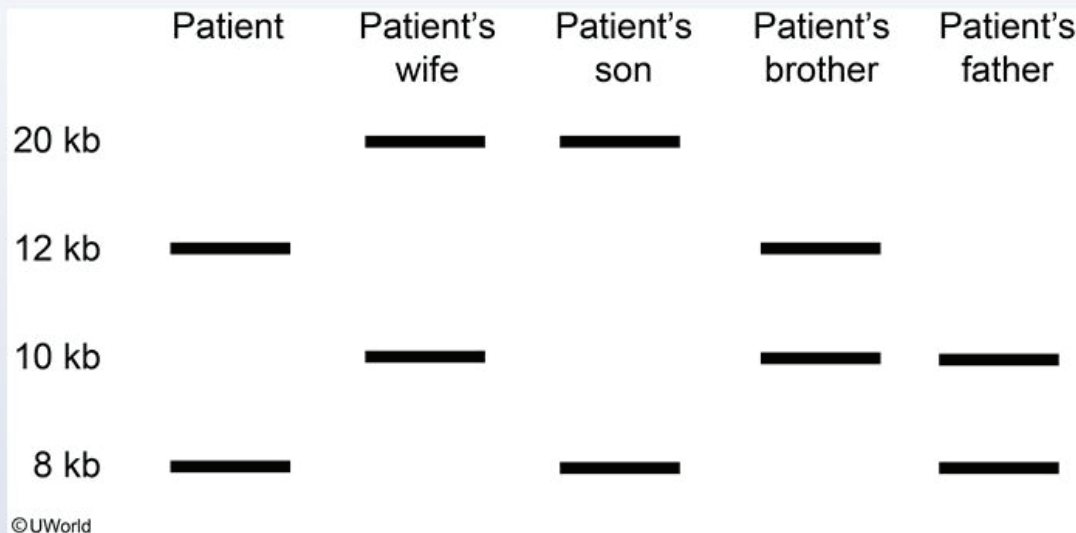


Text Zoom



Settings

A 34-year-old man is found to have an LDL level of 310 mg/dL and a normal serum triglyceride level. His father suffered a myocardial infarction at age 39, and his paternal grandfather died of a heart attack at age 40. The patient's wife has a normal lipid profile. DNA samples are obtained from several family members for genetic analysis. Southern blotting of restriction fragments from a region containing the LDL receptor gene shows the following pattern:



0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



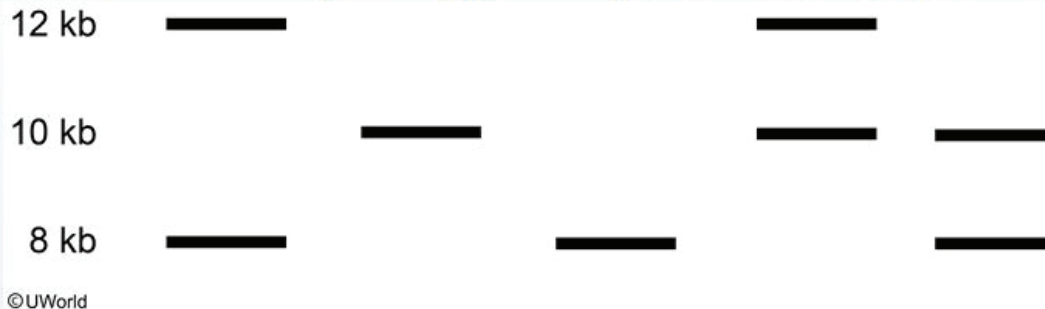
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Text Zoom



Settings



Which of the following statements best describes the DNA analysis results?

- ☐ A. The disease is transmitted in an X-linked recessive fashion
- ☐ B. The mutation is probably located in the 10 kb band
- ☐ C. The mutation is probably located in the 12 kb band
- ☐ D. The patient's brother most likely inherited the mutation
- ☐ E. The patient's son most likely inherited the mutation

Submit

Block Time Remaining: 00:48:50

<https://t.me/USMLEWorldStep1>

0



Feedback



Suspend



End Block



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

10 kb

8 kb

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Which of the following statements best describes the DNA analysis results?

- ☐ A. The disease is transmitted in an X-linked recessive fashion (3%)
- ☐ B. The mutation is probably located in the 10 kb band (1%)
- ☐ C. The mutation is probably located in the 12 kb band (1%)
- ☐ D. The patient's brother most likely inherited the mutation (2%)
- ☒ E. The patient's son most likely inherited the mutation (91%)

Correct

91%



01 min, 26 secs



12/19/2020

Block Time Remaining: 00:50:08

<https://t.me/USMLEWorldStep1>

Feedback

Suspend

End Block



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

This patient most likely has **heterozygous familial hypercholesterolemia**, an autosomal dominant LDL receptor defect that causes **high LDL levels** and increases the risk of **premature atherosclerosis**.

Homozygous familial hypercholesterolemia (a rarer and more severe form of the disease due to inheritance of 2 defective LDL receptor alleles) often presents with coronary heart disease in childhood/adolescence.

Southern blotting is a technique that can be used to detect DNA mutations. The process involves the following steps:

1. DNA extraction from the individual's cells
2. Restriction endonuclease digestion of the DNA sample into fragments
3. Gel electrophoresis to separate the various sizes of DNA fragments; larger fragments move slowly and shorter fragments move faster
4. DNA probe (a single-stranded segment of labeled DNA complementary to the gene of interest) to identify the target gene

Once the gene of interest is identified by the DNA probe, various family members' Southern blots can be compared. Because **both** the patient and his father are affected, the common DNA segment between them (**8 kb segment**) most likely represents the mutated gene. The patient's **son** also has the 8 kb segment, meaning that he is probably affected as well.





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

segment, meaning that he is probably affected as well.

(Choice A) Familial hypercholesterolemia is an autosomal dominant disorder. X-linked recessive mutations are transmitted from unaffected carrier mothers to their sons. Father-to-son transmission does not occur.

(Choices B and D) The patient (affected by the disease) does not possess the 10 kb segment, so this segment does not correspond to the mutated gene. The patient's brother inherited the 10 kb segment from his father (not the 8kb mutated segment), so he would not be affected.

(Choice C) The patient and his brother, but not their father, have a 12 kb segment on Southern blot analysis. Therefore, this segment was likely inherited from the mother and does not carry the mutation.

Educational objective:

Southern blotting is a technique used to identify DNA mutations. It involves restriction endonuclease digestion of sample DNA, gel electrophoresis, and gene identification with a labeled DNA probe.

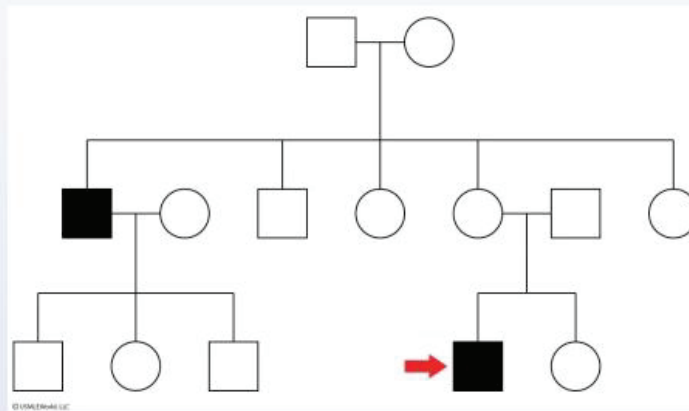
References

- Genetic defects causing familial hypercholesterolaemia: identification of deletions and duplications in the LDL-receptor gene and summary of all mutations found in patients attending the Hammersmith Hospital Lipid Clinic.



End Block

A 25-year-old man experiences severe intolerance to certain medications. On 2 occasions, his reactions to various drugs have necessitated hospital admission. His family pedigree with respect to this condition is shown below, with the red arrow indicating his position within the family.



Assuming that the genetic condition demonstrates complete penetrance and is rare in the general population, which of the following inheritance patterns is most likely?

- ☐ A. Autosomal dominant
- ☐ B. Autosomal recessive



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

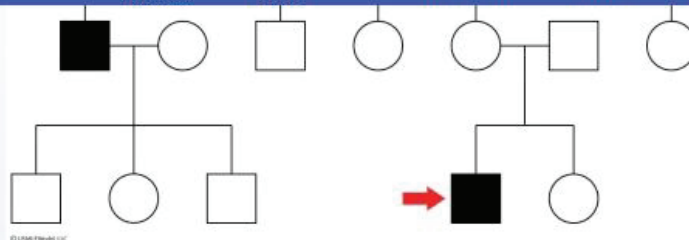
Notes

Calculator

Reverse Color

Text Zoom

Settings



Assuming that the genetic condition demonstrates complete penetrance and is rare in the general population, which of the following inheritance patterns is most likely?

- ☐ A. Autosomal dominant
- ☐ B. Autosomal recessive
- ☐ C. X-linked dominant
- ☐ D. X-linked recessive
- ☐ E. Mitochondrial

Submit

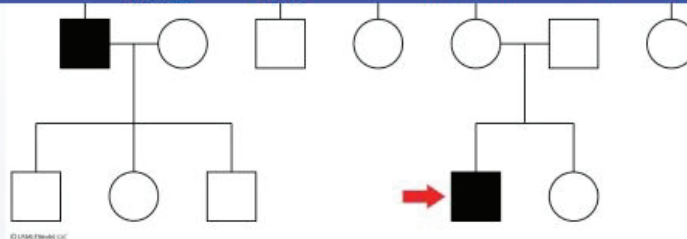
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<https://t.me/USMLEWorldStep1>

Feedback

Suspend

End Block



Assuming that the genetic condition demonstrates complete penetrance and is rare in the general population, which of the following inheritance patterns is most likely?

- ☐ A. Autosomal dominant (1%)
- ☐ B. Autosomal recessive (15%)
- ☐ C. X-linked dominant (4%)
- ☒ D. X-linked recessive (75%)
- ☐ E. Mitochondrial (3%)

Correct

75%

37 secs

10/03/2020

Block Time Remaining: 00:50:45

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Exhibit Display

X-linked recessive inheritance

Affected father

		Mother			
		X		X	
Father	X ^d	XX ^d		XX ^d	All daughters are carriers
	Y	XY		XY	All sons are normal

Carrier mother

		Mother			
		X		X ^d	
Father	X	XX		XX ^d	Daughters have 50% chance of becoming carriers
	Y	XY		X ^d Y	Sons have 50% chance of being affected

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Zoom In

Zoom Out

Reset

New | Existing

My Notebook



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

The pedigree shows that only males are affected by the drug intolerance. Specifically, **male offspring of unaffected parents** are affected. There is no evidence of male-to-male transmission. This pattern is most consistent with X-linked recessive inheritance from an asymptomatic carrier female in the first generation.

In **X-linked recessive inheritance**:

1. Affected males will always produce unaffected sons and carrier daughters.
2. Carrier females have a 50% chance of producing an affected son or carrier daughter.

G6PD deficiency, which causes acute hemolytic anemia on exposure to oxidant drugs, follows an X-linked recessive pattern of inheritance.

(Choice A) With autosomal dominant inheritance, affected individuals have at least 1 parent that is also affected.

(Choice B) In autosomal recessive inheritance, both parents must at least be carriers (heterozygous) for the mutation in order to produce affected offspring. However, the father of the marked individual comes from *outside the family* and would be unlikely to carry the mutation (the question states the mutation is rare in the general population).

(Choice C) In **X-linked dominant inheritance**, affected individuals have at least 1 parent (of either sex) that is also affected. An affected male will always produce affected daughters, but none of his sons will be





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

from *outside the family* and would be unlikely to carry the mutation (the question states the mutation is rare in the general population).

(Choice C) In **X-linked dominant inheritance**, affected individuals have at least 1 parent (of either sex) that is also affected. An affected male will always produce affected daughters, but none of his sons will be affected.

(Choice E) Conditions with mitochondrial inheritance are transmitted only by females. All of an affected female's offspring are likely to show signs of the disease.

Educational objective:

In X-linked recessive inheritance 1) affected males will always produce *unaffected* sons and *carrier* daughters, and 2) carrier females have a 50% chance of producing *affected* sons and *carrier* daughters. G6PD deficiency follows this inheritance pattern and causes acute hemolytic anemia in response to oxidant drugs.

Genetics

Genetics (General Principles)

Genetic inheritance

Subject

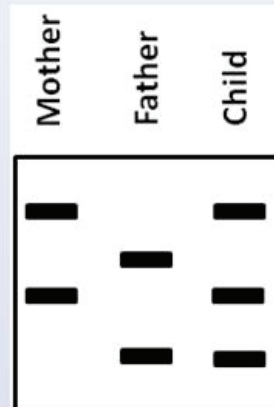
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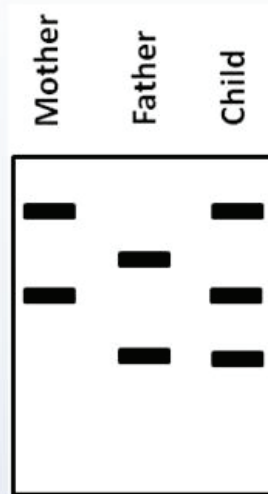
Topic

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An infant born to a 34-year-old woman has a flat facial profile, prominent epicanthal folds, and a holosystolic murmur heard loudest at the left sternal border. Karyotype analysis is consistent with trisomy 21. Maternal and paternal karyotypes are normal. A restriction fragment length polymorphism (RFLP) analysis is conducted to determine the parental origin of the extra chromosome. DNA samples from the child, mother, and father are obtained and the DNA is fragmented with a restriction enzyme. The fragments are then sorted by size using the Southern blot technique. Labeling is done using a probe that binds to a specific DNA sequence close to the centromere of chromosome 21. RFLP analysis for the child, mother, and father is shown below.





In which of the following meiosis events did the nondisjunction most likely occur?

- ☐ A. Maternal meiosis I
- ☒ B. Maternal meiosis II
- ☐ C. Paternal meiosis I
- ☐ D. Paternal meiosis II



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

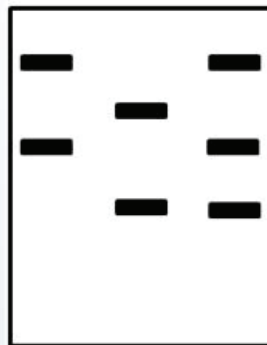
Notes

Calculator

Reverse Color

Text Zoom

Settings



In which of the following meiosis events did the nondisjunction most likely occur?

- ☐ A. Maternal meiosis I
- ☐ B. Maternal meiosis II
- ☐ C. Paternal meiosis I
- ☐ D. Paternal meiosis II

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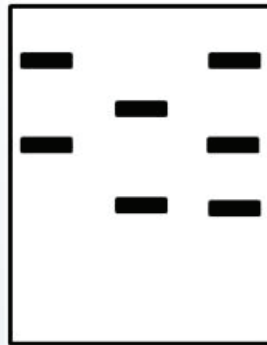
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Feedback

Suspend

End Block



In which of the following meiosis events did the nondisjunction most likely occur?

- ☒ A. Maternal meiosis I (52%)
- ☐ B. Maternal meiosis II (36%)
- ☐ C. Paternal meiosis I (5%)
- ☐ D. Paternal meiosis II (5%)

Incorrect

Correct answer

52%

01 min, 16 secs

12/22/2020

Block Time Remaining: 00:52:01

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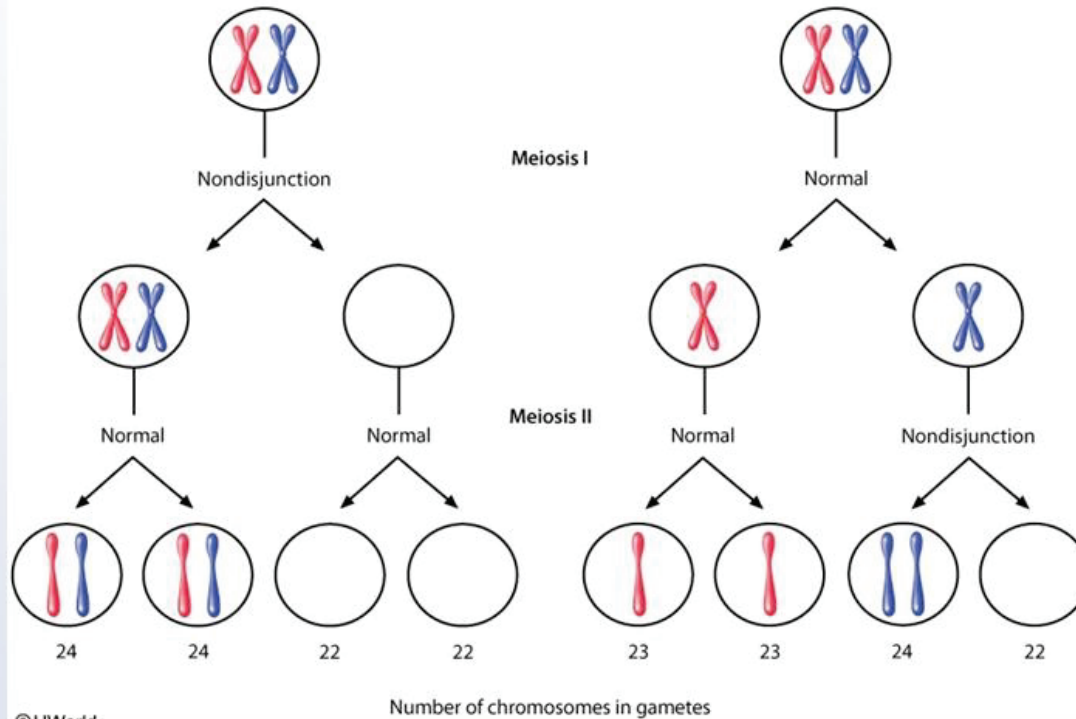


Feedback

Suspend

End Block

Nondisjunction in meiosis



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Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

Nondisjunction is the **failure of chromosome pairs to separate** properly during cell division. This could be due to a failure of **homologous chromosomes** to separate in **meiosis I** or a failure of **sister chromatids** to separate during **meiosis II or mitosis**. In monosomy, a single chromosome is lost. In trisomy, a single chromosome is gained. **Monosomies or trisomies** can result from nondisjunction in meiosis I or II.

Restriction fragment length polymorphism (RFLP) analysis shows that both parents demonstrate 2 bands. Each parental band represents a homologous chromosome 21. The child has 3 bands, indicating that he has 3 different versions of chromosome 21 that he obtained from his parents. He received the lower band from the father and both of the upper bands from the mother. The fact that he received 2 different bands from the mother indicates that he inherited both of her homologous chromosomes. Therefore, the problem occurred in the mother during meiosis I, when homologous chromosomes are separated. In fact, the vast majority of **Down syndrome** cases arise due to nondisjunction during maternal meiosis I.

(Choice B) If the mother had a failure in meiosis II, the child's RFLP analysis would reveal only two bands ([see example](#)). There would be a single band from the father and a darker, thicker band from the mother. The darker, thicker band signifies the inheritance of both sister chromatids, which will produce equal-size restriction fragments (but twice the normal amount).



0



Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color

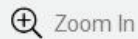
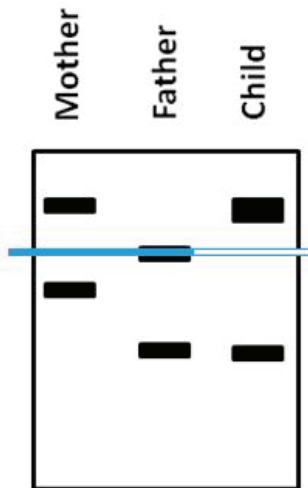


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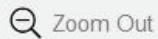


Settings

Exhibit Display



Zoom In



Zoom Out



Reset



New



Existing



My Notebook

My Notebook





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

(Choice B) If the mother had a failure in meiosis II, the child's RFLP analysis would reveal only two bands (see example). There would be a single band from the father and a darker, thicker band from the mother. The darker, thicker band signifies the inheritance of both sister chromatids, which will produce equal-size restriction fragments (but twice the normal amount).

(Choice C) If the father had a failure in meiosis I, the child's RFLP analysis would reveal 3 bands (see example). In this instance, there would be a single band inherited from the mother with two bands inherited from the father.

(Choice D) If the father had a failure in meiosis II, the child's RFLP analysis would reveal two bands (see example). In this instance, there would be a single band inherited from the mother and a second band from the father. The father's band would be darker and thicker, signifying the inheritance of both sister chromatids.

Educational objective:

Nondisjunction is the failure of chromosome pairs to separate properly during cell division. This could be due to a failure of homologous chromosomes to separate in meiosis I or a failure of sister chromatids to separate during meiosis II or mitosis.



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Feedback



Suspend



End Block

Exhibit Display

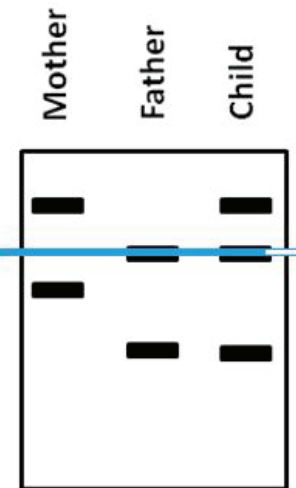
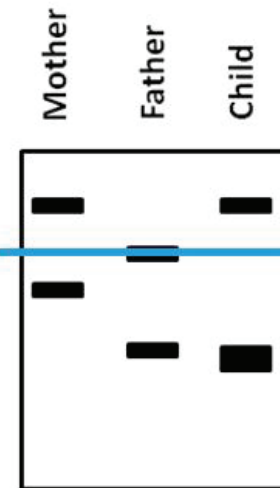


Exhibit Display



- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12
- 13
- 14
- 15
- 16
- 17
- 18
- 19
- 20
- 21



A study is undertaken to map the HLA-DQ loci in a population with a high incidence of celiac sprue. High-resolution HLA typing of the DQA1 and DQB1 loci is performed using polymerase chain reaction sequencing. The frequency of the DQA1*0501-DQB1*0201 haplotype, strongly implicated in autoimmunity, is found to be 0.2. However, in the same population, the frequency of the DQA1*0501 allele is 0.3 and the frequency of the DQB1*0201 allele is 0.2. Which of the following best explains the observed DQA1*0501-DQB1*0201 haplotype frequency in this population?

- ☐ A. Heteroplasmy
- ☐ B. Increased penetrance
- ☐ C. Linkage disequilibrium
- ☐ D. Pleiotropy
- ☐ E. Segregation

Submit



A study is undertaken to map the HLA-DQ loci in a population with a high incidence of celiac sprue. High-resolution HLA typing of the DQA1 and DQB1 loci is performed using polymerase chain reaction sequencing. The frequency of the DQA1*0501-DQB1*0201 haplotype, strongly implicated in autoimmunity, is found to be 0.2. However, in the same population, the frequency of the DQA1*0501 allele is 0.3 and the frequency of the DQB1*0201 allele is 0.2. Which of the following best explains the observed DQA1*0501-DQB1*0201 haplotype frequency in this population?

- ☐ A. Heteroplasmy (11%)
- ☐ B. Increased penetrance (8%)
- ☒ C. Linkage disequilibrium (60%)
- ☐ D. Pleiotropy (13%)
- ☐ E. Segregation (7%)

Correct



60%

Answered correctly



02 mins, 12 secs

Time Spent



02/13/2021

Last Updated

Block Time Remaining: 00:02:12

TUTOR

<https://t.me/USMLEWorldStep1>

1



Feedback



Suspend



End Block

1

• 2

• 3

• 4

• 5

• 6

• 7

• 8

• 9

• 10

• 11

• 12

• 13

• 14

• 15

• 16

• 17

• 18

• 19

• 20

• 21

Item 1 of 21

Question Id: 8283

Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

Exhibit Display

Parental genome

Linkage equilibrium

A

a

B

b

Genes on separate chromosomes segregate independently

AB

ab

Ab

aB

Equal frequencies for all haplotypes

Parental genome

Linkage disequilibrium

A

a

B

b

Genes in close proximity become linked

AB

ab

Ab

aB

↑ Frequency

↓ Frequency

Haplotype frequency unequal

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Zoom In

Zoom Out

Reset

New

Existing

My Notebook

Block Time Remaining: 00:02:12

TUTOR

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1

Feedback

Suspend

End Block

1

• 2

• 3

• 4

• 5

• 6

• 7

• 8

• 9

• 10

• 11

• 12

• 13

• 14

• 15

• 16

• 17

• 18

• 19

• 20

• 21

Item 1 of 21

Question Id: 8283

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become linked

Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

Two genetic loci are said to be in **linkage disequilibrium** when their respective alleles are **inherited together** in the same gamete (haplotype) **more or less often than expected** by chance alone given their corresponding allele frequencies. Although linkage disequilibrium is often the result of **physical proximity** of genes on the same chromosome, it does not always imply physical linkage between the allelic loci.

To estimate the expected probability of 2 alleles from separate loci appearing together, multiply their occurrence rates. Note that the Hardy-Weinberg principle ($2pq$) is not applicable when considering alleles at different loci.

DQA1*0501-DQB1*0201	= [Frequency of DQA1*0501] ×
haplotype frequency	[Frequency of DQB1*0201]
	= 0.3 × 0.2
	= 0.06

In this example, the observed frequency of both alleles being inherited together is **0.2**, which is greater than the expected frequency of 0.06; therefore, the population is said to be in linkage disequilibrium. This disequilibrium is explained by the close proximity of the HLA-DQA1 and HLA-DQB1 loci that code for α and β chains of class II major histocompatibility complex.

Block Time Remaining: 00:02:12

TUTOR

<https://t.me/USMLEWorldStep1>

1

Feedback

Suspend

End Block

1

• 2

• 3

• 4

• 5

• 6

• 7

• 8

• 9

• 10

• 11

• 12

• 13

• 14

• 15

• 16

• 17

• 18

• 19

• 20

• 21

Item 1 of 21

Question Id: 8283

Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

= 0.06

In this example, the observed frequency of both alleles being inherited together is **0.2**, which is greater than the expected frequency of 0.06; therefore, the population is said to be in linkage disequilibrium. This disequilibrium is explained by the close proximity of the HLA-DQA1 and HLA-DQB1 loci that code for α and β chains of class II major histocompatibility complex.

(Choice A) Heteroplasmy describes the presence of different mitochondrial genomes (eg, mutated and wild type) within a single cell. The severity of mitochondrial diseases is often related to the proportion of abnormal to normal mitochondria.

(Choice B) Penetrance is the proportion of people with a given genotype who express its associated phenotype. If all individuals with a given gene express its phenotype, that gene is said to have full penetrance.

(Choice D) Pleiotropy is the occurrence of multiple phenotypic manifestations, often in different organ systems, which result from a mutation in a single gene.

(Choice E) The law of segregation describes the phenomenon in which gametogenesis results in the separation of paired chromosomes so that the offspring inherit only half of each parent's genetic composition.

Block Time Remaining: 00:02:12

TUTOR

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1

Feedback

Suspend

End Block

1

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• 9

• 10

• 11

• 12

• 13

• 14

• 15

• 16

• 17

• 18

• 19

• 20

• 21

Item 1 of 21

Question Id: 8283

Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

(Choice B) Penetrance is the proportion of people with a given genotype who express its associated phenotype. If all individuals with a given gene express its phenotype, that gene is said to have full penetrance.

(Choice D) Pleiotropy is the occurrence of multiple phenotypic manifestations, often in different organ systems, which result from a mutation in a single gene.

(Choice E) The law of segregation describes the phenomenon in which gametogenesis results in the separation of paired chromosomes so that the offspring inherit only half of each parent's genetic composition.

Educational objective:

Two allele loci are said to be in linkage disequilibrium when a pair of alleles are inherited together in the same gamete (haplotype) more often or less often than would be expected given random pairing. This most often occurs when the genes are in close physical proximity on the same chromosome.

References

- [Gene polymorphisms, inflammatory diseases and cancer.](#)
- [Linkage disequilibrium and its expectation in human populations.](#)

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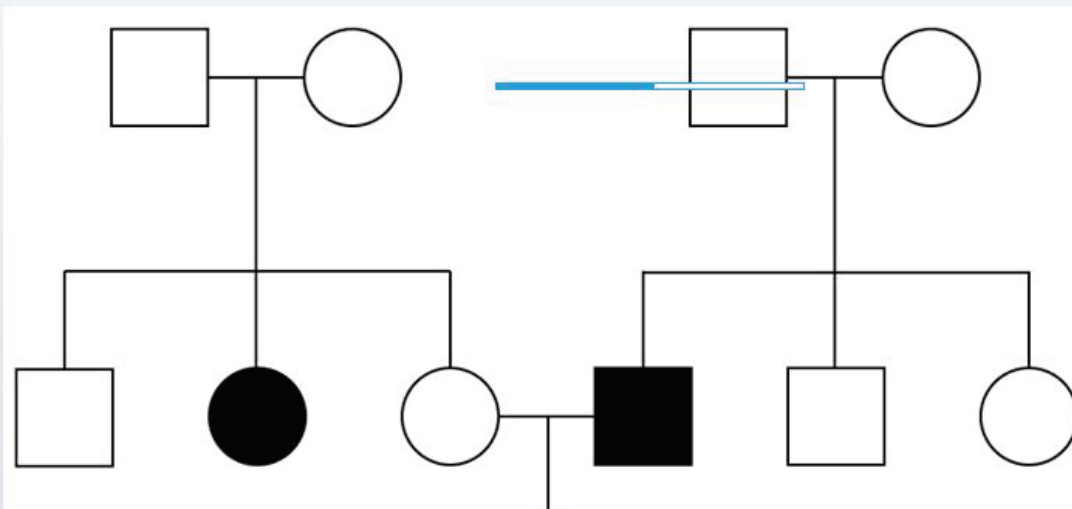
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A young couple has undergone a successful in vitro fertilization procedure. The father has cystic fibrosis and the mother has a sister with cystic fibrosis. The father as well as the mother's sister are both known to have $\Delta F508$ mutations, but the mother's carrier status is unknown. Before making the decision to conceive, the couple underwent extensive genetic counseling regarding the potential risks of having a child with cystic fibrosis. The family pedigree is diagrammed below with the unborn child marked by the red arrow.



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21

Item 2 of 21
Question Id: 1790

Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

Exhibit Display

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Zoom Out

Reset

New | Existing

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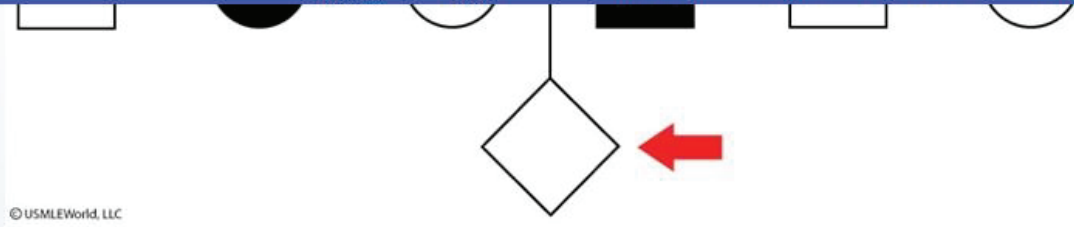
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What is the probability that the unborn child will have cystic fibrosis?

- ☐ A. 1/16
- ☐ B. 1/8
- ☐ C. 1/4
- ☐ D. 1/3
- ☒ E. 2/3
- ☐ F. 3/4

Submit

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What is the probability that the unborn child will have cystic fibrosis?

- ☐ A. 1/16 (3%)
- ☒ B. 1/8 (12%)
- ☐ C. 1/4 (31%)
- ☒ D. 1/3 (35%)
- ☐ E. 2/3 (11%)
- ☐ F. 3/4 (5%)

Incorrect

Correct answer

35%

Answered correctly



01 min, 58 secs

Time Spent



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Block Time Remaining: 00:04:10

TUTOR

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Feedback



Suspend



End Block



Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom

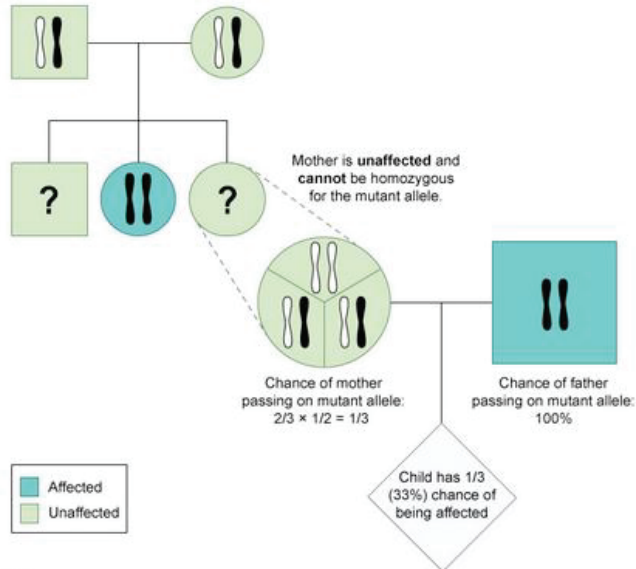


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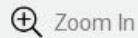
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Probability of the child having cystic fibrosis

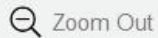
Unaffected grandparents with a diseased child are likely heterozygous for the mutant allele.



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Feedback



Suspend



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Cystic fibrosis (CF) results from an **autosomal recessive** defect in the CF transmembrane conductance regulator (*CFTR*) gene. Although most men with CF are infertile due to congenital absence of the vas deferens, they are **not sterile** and can have children via assisted reproductive technology.

Calculating the probability that the unborn child will have CF can be done by analyzing the above pedigree as follows:

1. Because the **father** is homozygous for the mutant *CFTR* allele, he will **always** transmit the mutant allele to his offspring.
2. Because the **mother** has an affected sibling and neither of her parents is affected, she most likely had 2 heterozygous carrier parents. Therefore, the mother's 4 possible genotypes are: homozygous for the normal allele, heterozygous with her mother's mutant allele, heterozygous with her father's mutant allele, and homozygous for the mutant allele. However, the mother does **not have CF** and therefore is **not homozygous for the mutant allele**. This leaves 3 possible genotypes for the mother. Two of the 3 remaining genotypes result in her being a **carrier** for the mutant *CFTR* allele, while the last one results in her being homozygous normal. Therefore, the mother's probability of being a carrier equals **2/3**.

3. If the mother is a carrier (2/3 chance), the probability that she will transmit the mutant allele to the child



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21

Item 2 of 21

Question Id: 1790

Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

results in her being homozygous normal. Therefore, the mother's probability of being a carrier equals $\frac{2}{3}$.

3. If the mother is a carrier ($\frac{2}{3}$ chance), the probability that she will transmit the mutant allele to the child is 1 in 2. As a result, the probability that the child will inherit a mutant allele from the mother (and therefore have CF as the father will always contribute a mutant allele) is: $\frac{2}{3} \times \frac{1}{2} = \frac{1}{3}$.

Educational objective:

The probability that an autosomal recessive disease will be transmitted to a child can be calculated based on the maternal and paternal pedigrees. An unaffected individual (with unaffected parents) who has a sibling affected by an autosomal recessive condition has a $\frac{2}{3}$ chance of being a carrier for that condition.

References

- Genetic counseling issues in cystic fibrosis.
- Cystic fibrosis and fertility.

Genetics

Genetics (General Principles)

Genetic inheritance

Subject

System

Topic

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A 26-year-old woman comes to the office for follow-up. The patient and her husband want to have a child, and she inquires about the risk of certain genetic conditions, including cystic fibrosis (CF). The patient is from a small city with a stable Caucasian population, where the carrier frequency for CF is 1/30 Caucasian individuals. Her husband is from a nearby community, where CF carrier frequency in individuals of Asian descent is 1/100. Both the patient, who is Caucasian, and her husband, who is of Asian descent, are healthy. What is the probability that a child born to a mother from the Caucasian community and a father from the Asian community will have the disease?

- ☐ A. 1/900
- ☐ B. 1/1,000
- ☐ C. 1/3,000
- ☐ D. 1/6,000
- ☐ E. 1/12,000

Submit



A 26-year-old woman comes to the office for follow-up. The patient and her husband want to have a child, and she inquires about the risk of certain genetic conditions, including **cystic fibrosis** (CF). The patient is from a small city with a stable Caucasian population, where the carrier frequency for CF is 1/30 Caucasian individuals. Her husband is from a nearby community, where CF carrier frequency in individuals of Asian descent is 1/100. Both the patient, who is Caucasian, and her husband, who is of Asian descent, are healthy. What is the probability that a child born to a mother from the Caucasian community and a father from the Asian community will have the disease?

- ☐ A. 1/900 (3%)
- ☐ B. 1/1,000 (2%)
- ☐ C. 1/3,000 (29%)
- ☐ D. 1/6,000 (6%)
- ☒ E. 1/12,000 (58%)



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17

18

19

20

21

Item 3 of 21

Question Id: 1791

Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

Exhibit Display

Autosomal recessive inheritance

Carrier parent (Aa)

A

a

A

Aa

Normal child

Carrier child

a

Aa

Carrier child

aa

Affected child

Offspring have 25% chance of being affected

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Reset

New

Existing

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Block Time Remaining: 00:05:45

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Feedback

Suspend

End Block



Ourspring have 25% chance of being affected

Cystic fibrosis (CF) is an **autosomal recessive** disease. The patient, who is Caucasian, has a 1/30 probability of carrying the mutant *CFTR* allele and her husband, who is of Asian descent, has a 1/100 probability of carrying the same allele. If a parent is a **carrier**, the probability that the child will inherit the mutant allele from that parent is 1/2. However, to develop CF, the child must independently inherit a mutant allele from each parent ($1/2 \times 1/2 = 1/4$ probability). Therefore:

$$P(\text{affected child}) = 1/4 \times P(\text{carrier mother}) \times P(\text{carrier father}) = 1/4 \times 1/30 \times 1/100 = 1/12,000.$$

An equivalent solution would be to state that the probability that the mother is a carrier and will transmit the mutant allele is ($1/30 \times 1/2$) and the probability that the father is a carrier and will transmit the mutant allele is ($1/100 \times 1/2$). The probability that both events will occur, producing a child with CF, is the product of the probabilities of these independent events = ($1/30 \times 1/2$) \times ($1/100 \times 1/2$) = 1/12,000.

Educational objective:

The probability that a child of parents from 2 populations with different mutant allele carrier frequencies will inherit an autosomal recessive disease is 25% multiplied by the carrier frequencies.





A pharmaceutical researcher performs preclinical testing on a novel chemotherapeutic drug. When rat embryos are exposed to this drug during an early stage of organogenesis, they develop severe skeletal malformations. Further genetic analysis reveals that the drug causes mutations in numerous homeobox genes containing highly conserved 180 base pair DNA sequences. The genes affected by this drug most likely code for which of the following proteins?

- ☐ A. Cell surface receptors
- ☐ B. Cytoplasmic enzymes
- ☐ C. DNA replication enzymes
- ☐ D. Structural proteins
- ☒ E. Transcription regulators
- ☐ F. Transport proteins

Submit



A pharmaceutical researcher performs preclinical testing on a novel **chemotherapeutic drug**. When rat embryos are exposed to this drug during an early stage of organogenesis, they develop severe **skeletal malformations**. Further genetic analysis reveals that the drug causes mutations in numerous **homeobox** genes containing highly conserved 180 base pair DNA sequences. The genes affected by this drug most likely code for which of the following proteins?

- ☐ A. Cell surface receptors (4%)
- ☐ B. Cytoplasmic enzymes (1%)
- ☐ C. DNA replication enzymes (8%)
- ☐ D. Structural proteins (25%)
- ☒ E. Transcription regulators (56%)
- ☐ F. Transport proteins (3%)

Correct



56%

Answered correctly



46 secs

Time Spent



02/05/2021

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Block Time Remaining: 00:06:31

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Homeobox (HOX) genes

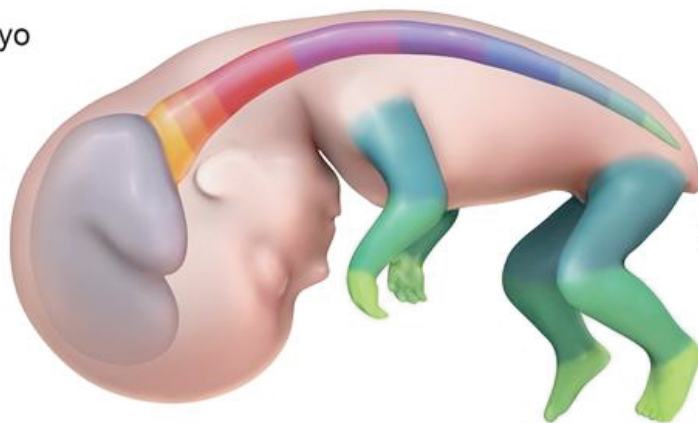
DNA



Human embryo

Cranial

Caudal



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A homeobox is a highly conserved DNA sequence that is usually about 180 nucleotides in length. A gene containing a homeobox sequence is called a **homeobox** or **hox gene**. These genes typically code for **transcription factors** that bind to regulatory regions on DNA, altering the expression of genes involved in the segmental organization of the embryo. Proper morphogenesis ensures that tissues, organs, and structural elements of the body are formed in the correct position along the cranio-caudal axis. Homeobox gene mutations interrupt this developmental process, often resulting in severe abnormalities such as skeletal malformations and improperly positioned limbs and appendages.

(Choices A, B, C, D, and F) Homeobox genes do not typically encode cell surface receptors, cytoplasmic enzymes, DNA replication enzymes, structural proteins, or transport proteins.

Educational objective:

Homeobox genes encode DNA-binding transcription factors that play an important role in the segmental organization of the embryo along the cranio-caudal axis.

References

- [The regulation of Hox gene expression during animal development.](#)



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10

11

12

13

14

15

16

17

18

19

20

21

Item 5 of 21

Question Id: 1610

Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

A 1-hour-old girl born to a 40-year-old woman is brought to the nursery for evaluation. The pregnancy and delivery were uncomplicated. Physical examination shows mid-face hypoplasia with a flat nasal bridge, up-slanting palpebral fissures, a small mouth, and a single palmar crease bilaterally. Cardiac auscultation reveals a blowing holosystolic murmur heard best along the sternal border. Which of the following abnormalities is most likely to be present in this patient?

☐ A. Aberrant genomic imprinting

☐ B. Mosaicism

☐ C. Partial deletion

☐ D. Triplet expansion

☐ E. Uniparental disomy

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A 1-hour-old girl born to a 40-year-old woman is brought to the nursery for evaluation. The pregnancy and delivery were uncomplicated. Physical examination shows mid-face **hypoplasia** with a flat nasal **bridge**, up-slanting palpebral **fissures**, a small mouth, and a single **palmar crease** bilaterally. Cardiac auscultation reveals a blowing holosystolic murmur heard best along the sternal border. Which of the following abnormalities is most likely to be present in this patient?

- ☐ A. ~~Aberrant genomic imprinting~~ (2%)
- ✓ ☒ B. Mosaicism (46%)
- ☐ C. ~~Partial deletion~~ (5%)
- ☐ D. ~~Triplet expansion~~ (12%)
- ☐ E. Uniparental disomy (33%)

Correct



46%

Answered correctly



44 secs

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10/06/2020

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Inheritance of Down syndrome

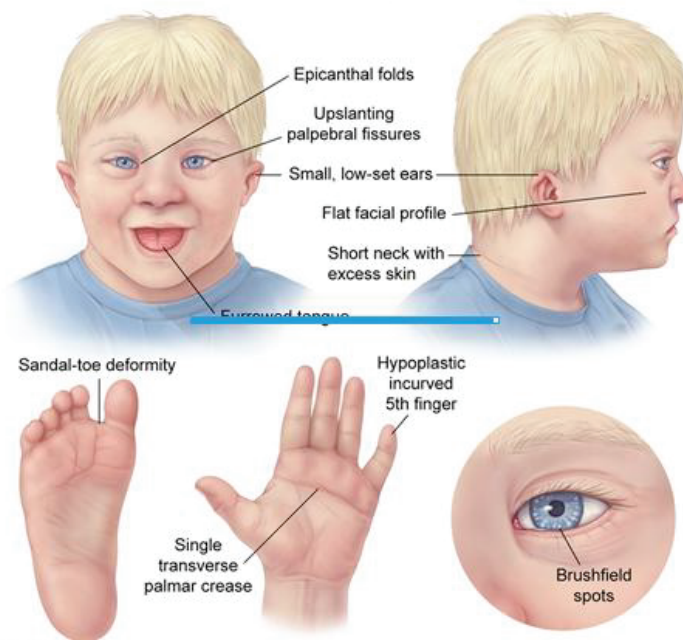
Mechanism	Pathogenesis	Recurrence risk
Meiotic nondisjunction (~95%)	<ul style="list-style-type: none"> Extra copy of chromosome 21 present in every cell 	Based on maternal age
Unbalanced translocation	<ul style="list-style-type: none"> All or part of additional chromosome 21 attached to another chromosome 	High if balanced translocation is present in one parent
Mosaicism	<ul style="list-style-type: none"> Some (not all) cells have an extra copy of chromosome 21 Nondisjunction event in early embryonic life 	Similar to normal population

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This child has many of the characteristic features of **Down syndrome** (DS), a condition that results from an **increased gene dosage** effect due to an **extra copy** of chromosome 21. Three cytogenetic abnormalities can lead to DS:

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Features of Down syndrome



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New | Existing

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can lead to DS:

- **Meiotic nondisjunction** accounts for nearly 95% of DS cases. Failure of homologous chromosomes or sister chromatids to separate during meiosis can result in the inheritance of 3 copies of chromosome 21 in one daughter cell (trisomy) and 1 copy in the other daughter cell (monosomy). Nondisjunction during meiosis is almost always of maternal origin.
- **Unbalanced translocations** account for 2%-3% of DS cases. These individuals have 46 chromosomes, but have extra genetic material (consisting of duplicate chromosome 21 genes) attached to one of their chromosomes. Approximately one third of these cases are due to a balanced translocation in one parent, which confers a high recurrence risk.
- **Mosaicism** accounts for <2% of DS cases. Affected individuals have 2 distinct cell lines as a result of **nondisjunction during mitosis**: one with a normal genotype and one with trisomy 21. The proportion of affected cells determines the severity of DS features.

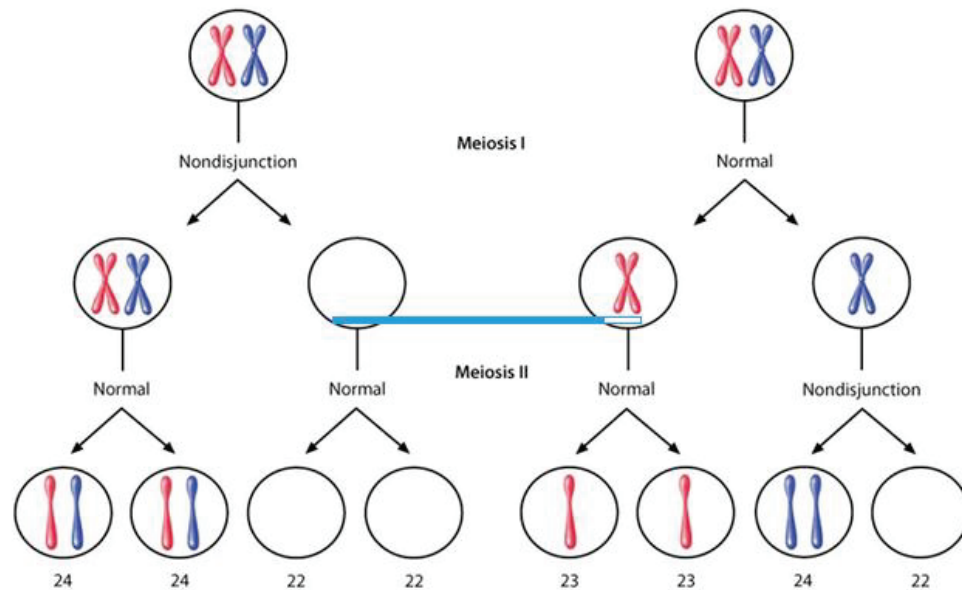
Of the available answer options, only mosaicism is consistent with a **third copy** of chromosome 21 existing in at least a portion of the patient's cells.

(Choices A and E) Genomic imprinting is a normal process that refers to selective activation of gene expression depending on the parent of origin. Aberrant imprinting occurs with uniparental disomy, or when



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Nondisjunction in meiosis



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Number of chromosomes in gametes

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Zoom Out

Reset

New | Existing

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expression depending on the parent of origin. Aberrant imprinting occurs with uniparental disomy, or when



in at least a portion of the patient's cells.

(Choices A and E) Genomic imprinting is a normal process that refers to selective activation of gene expression depending on the parent of origin. Aberrant imprinting occurs with uniparental disomy, or when a person receives **2 copies** of a chromosome from the same parent and no copy from the other parent. Prader-Willi syndrome and Angelman syndrome (15q) are examples of conditions caused by dysfunctional imprinting due to uniparental disomy.

(Choice C) Many genetic syndromes are caused by deletions (loss of genetic material). Cri du chat syndrome (5p deletion) is an example of a syndrome caused by a partial deletion of chromosome 5.

(Choice D) Increased trinucleotide repeats (triplet expansion) on certain genes can lead to silencing of a gene or synthesis of an abnormal gene product. Huntington disease and fragile X syndrome are examples of conditions caused by triplet expansion.

Educational objective:

Common findings in Down syndrome include cognitive impairment, facial dysmorphism, and cardiac defects; 95% of cases are caused by the presence of an extra chromosome 21 (trisomy) resulting from nondisjunction. Unbalanced Robertsonian translocations or mosaicism are less common causes.

References





A 10-year-old boy is brought to the emergency department for new swelling in his right leg. He has a history of lens dislocation and intellectual disability. Physical examination demonstrates moderate, pitting edema from his right calf to his right thigh and a normal left lower extremity. In addition, the patient has a caved-in appearing chest wall. He has no family members with similar conditions. Ultrasound reveals a deep venous thrombosis in his right femoral vein. Further genetic testing reveals a single missense mutation in the gene coding for cystathionine beta-synthase enzyme. Which of the following is the most likely explanation for this patient's genetic defect affecting multiple tissues?

- ☐ A. Dominant negative mutation
- ☐ B. Genetic linkage
- ☐ C. Incomplete penetrance
- ☐ D. Locus heterogeneity
- ☐ E. Pleiotropy
- ☐ F. Polyploidy
- ☐ G. Segregation



edema from his right calf to his right thigh and a normal left lower extremity. In addition, the patient has a caved-in appearing chest wall. He has no family members with similar conditions. Ultrasound reveals a deep venous thrombosis in his right femoral vein. Further genetic testing reveals a single missense mutation in the gene coding for cystathionine beta-synthase enzyme. Which of the following is the most likely explanation for this patient's genetic defect affecting multiple tissues?

- ☐ A. Dominant negative mutation (5%)
- ☐ B. Genetic linkage (3%)
- ☐ C. Incomplete penetrance (2%)
- ☐ D. Locus heterogeneity (10%)
- ☒ E. Pleiotropy (74%)
- ☐ F. Polyploidy (3%)
- ☐ G. Segregation (0%)

Correct

74% Answered correctly

02 mins, 18 secs Time Spent

02/01/2021 Last Updated



This patient presenting with skeletal abnormalities, lens dislocation, intellectual deficits, vascular thromboses, and a genetic defect in the cystathionine beta-synthase enzyme likely has [homocystinuria](#).

The occurrence of **multiple**, seemingly unrelated **phenotypic manifestations**, often in different organ systems, as a result of a **single genetic defect** is termed **pleiotropy**. Most syndromic genetic illnesses including homocystinuria exhibit pleiotropy.

(Choice A) Dominant negative mutations occur when an abnormal gene negatively affects the product of the wild-type gene in the same cell. For example, certain oncogene *p53* mutations can lead to translation of a protein product that prevents wild-type *p53* from binding to the promoter of its target genes.

(Choice B) Genetic linkage describes the tendency of alleles located near one another on the same chromosome to be inherited jointly.

(Choice C) Penetrance refers to the proportion of individuals with a given genotype that express the associated phenotype. In incomplete penetrance, less than 100% of individuals with a given genotype express its associated phenotype.

(Choice D) Locus heterogeneity refers to the ability of one disease or trait to be caused by mutations in multiple different genes. An example is familial hypercholesterolemia, which can be caused by different mutations affecting cholesterol metabolism genes (eg, LDL receptor and PCSK9).





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

Exhibit Display

Features of homocystinuria

Pathogenesis

- Most commonly due to an autosomal recessive mutation causing cystathionine synthase deficiency

Clinical findings

- Optic lens dislocation
- Intellectual disability
- Marfanoid habitus (eg, elongated limbs & arachnodactyly)
- Thromboembolic complications

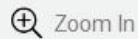
Diagnosis

- ↑ plasma and urinary homocystine levels

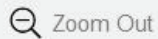
Treatment

- Pyridoxine (vitamin B6) administration
- Dietary methionine restriction & cysteine supplementation

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Feedback



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(Choice D) Locus heterogeneity refers to the ability of one disease or trait to be caused by mutations in multiple different genes. An example is familial hypercholesteremia, which can be caused by different mutations affecting cholesterol metabolism genes (eg, LDL receptor, apo B-100).

(Choice F) Polyploidy occurs when more than 2 complete sets of homologous chromosomes exist within an organism or cell. In a partial hydatidiform mole, for example, there are cells of nonstandard ploidy (typically 69,XXX; 69,XXY; or 69,XYY). The chromosomes in this case are derived from 1 haploid maternal set and 2 haploid paternal sets of chromosomes.

(Choice G) The law of segregation (Mendel's first law) describes the phenomenon whereby gametogenesis within the parent organism results in the separation of paired alleles so that each offspring inherits only half of each parent's genetic composition.

Educational objective:

Pleiotropy describes instances where multiple phenotypic manifestations result from a single genetic mutation. Most syndromic genetic illnesses exhibit pleiotropy.

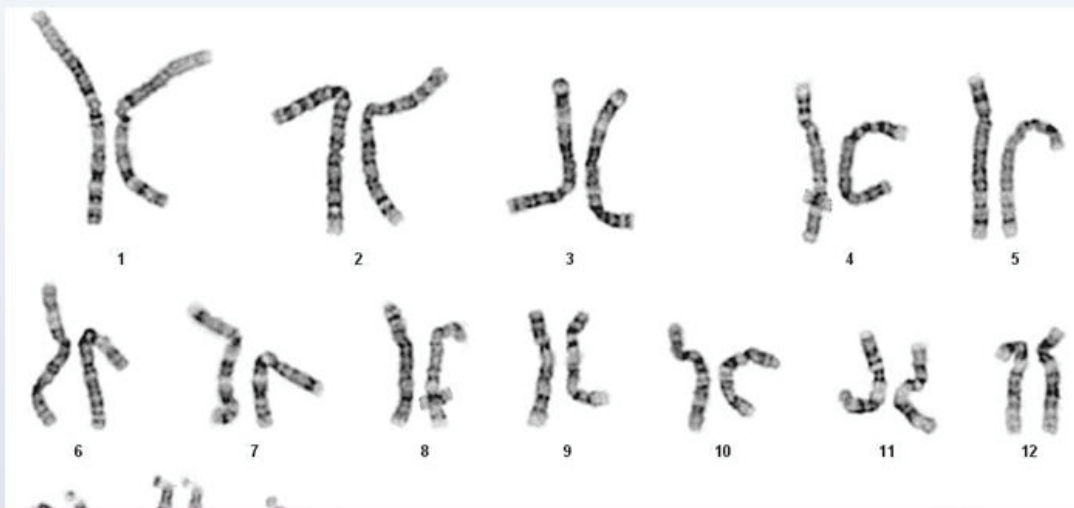
References

- [Pleiotropy in complex traits: challenges and strategies.](#)





A 35-year-old woman and her husband have been trying to conceive for more than a year and are being followed by an infertility specialist. The woman is found to have significant scarring and fibrosis involving her fallopian tubes secondary to pelvic inflammatory disease that she had at a young age. After a long struggle, the woman finally becomes pregnant. She gives birth to a boy who is evaluated by a pediatrician and found to have a flat nasal bridge, small mouth, and low-set ears. The pediatrician orders a karyotype analysis on the infant, which is shown below.



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Exhibit Display

Zoom In Zoom Out Reset New Existing My Notebook



The infant is most likely to be diagnosed with which of the following conditions?

- ☐ A. Acute lymphoblastic leukemia
- ☐ B. Chronic myelogenous leukemia
- ☐ C. Immotile cilia
- ☐ D. Macroorchidism
- ☐ E. Red blood cell sickling
- ☐ F. Rickets

Submit





The infant is most likely to be diagnosed with which of the following conditions?

- ☒ A. Acute lymphoblastic leukemia (85%)
- ☐ B. Chronic myelogenous leukemia (8%)
- ☐ C. Immotile cilia (1%)
- ☐ D. Macroorchidism (3%)
- ☐ E. Red blood cell sickling (0%)
- ☐ F. Rickets (0%)





This karyotype shows **trisomy 21** (47, XY, +21), which is diagnostic for **Down syndrome**, the most common genetic cause of congenital **intellectual disability**. In most cases, Down syndrome results from



This karyotype shows **trisomy 21** (47, XY, +21), which is diagnostic for **Down syndrome**, the most common genetic cause of congenital **intellectual disability**. In most cases, Down syndrome results from meiotic nondisjunction in the ovum; the parents themselves are usually genetically normal. **Advanced maternal age** is a risk factor for having a child with Down syndrome.

Individuals with Down syndrome are at an increased risk of developmental abnormalities (eg, cardiac septal defects, duodenal atresia) and health complications (eg, early-onset Alzheimer disease, ophthalmologic disorders). They also have **increased risk** of hematologic malignancies such as **acute lymphoblastic leukemia** and acute megakaryoblastic leukemia.

(Choice B) Chronic myelogenous leukemia is commonly associated with the Philadelphia chromosome (reciprocal translocation between the long arms of chromosomes 9 and 22). This translocation fuses the BCR gene on chromosome 22 to the ABL gene on chromosome 9, resulting in formation of the oncogenic BCR-ABL fusion gene on the shortened chromosome 22. Karyotype analysis shows elongation of chromosome 9 and shortening of chromosome 22.

(Choice C) Immotile cilia are found in Kartagener syndrome, a condition caused in most cases by an autosomal recessive mutation in the gene coding for the microtubule-associated protein dynein. Patients can have infertility, recurrent sinusitis, and bronchiectasis. Situs inversus may also be present.



(Choice C) Immotile cilia are found in Kartagener syndrome, a condition caused in most cases by an autosomal recessive mutation in the gene coding for the microtubule-associated protein dynein. Patients can have infertility, recurrent sinusitis, and bronchiectasis. Situs inversus may also be present.

(Choice D) Macroorchidism (ie, large testes) typically develops in pubertal boys with fragile X syndrome, the second most common genetic cause (and the most common inherited cause) of intellectual disability in males. On karyotype analysis, this X-linked disorder shows a discontinuity of staining on the long arm of the X chromosome.

(Choice E) Red blood cell sickling occurs in sickle cell anemia. The sickle cell mutation is localized to individual β -globin genes on chromosome 11 and does not result from trisomy 21.

(Choice F) Rickets can be caused by autosomal dominant, autosomal recessive, and X-linked mutations that affect calcium and phosphate metabolism and bone mineralization.

Educational objective:

Trisomy 21 is detectable by cytogenetic karyotype analysis and is the most common genetic cause of congenital intellectual disability. Patients with Down syndrome are at increased risk of developing acute lymphoblastic leukemia and acute megakaryoblastic leukemia.

References





A 26-year-old woman comes to the office with her husband for genetic counseling. She is pregnant with their second child, whose gender is unknown. Both parents are asymptomatic, but their firstborn 3-year-old son has recurrent episodes of anemia, jaundice, and painful swelling of the hands and feet. A blood sample is obtained from the boy, and hemoglobin electrophoresis is performed at alkaline pH. The results are shown in the image below.

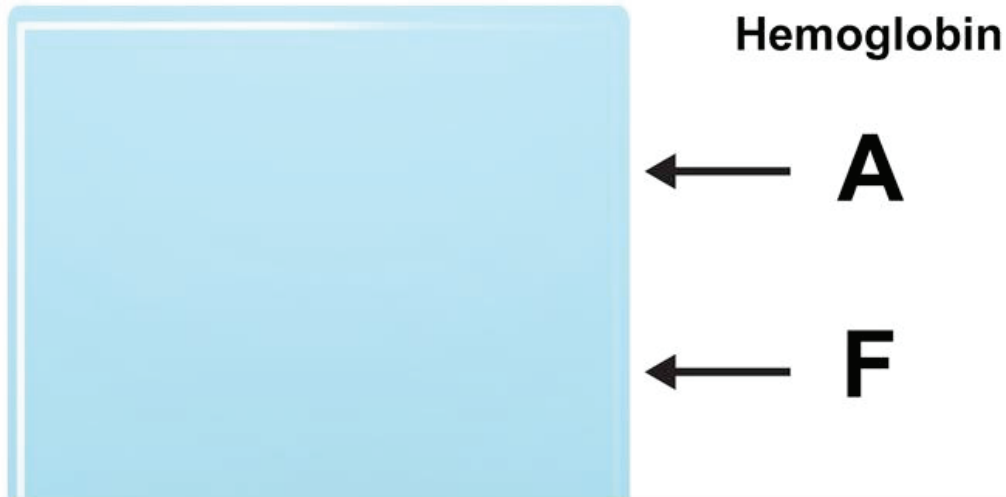
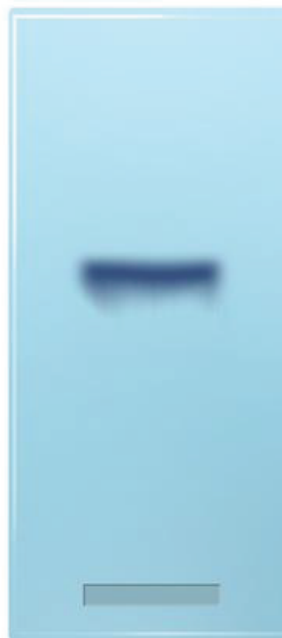


Exhibit Display



Hemoglobin

← A

← F

← S

← C

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Zoom In

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What is the probability that the unborn child will inherit one or more mutant alleles from the parents?

- ☐ A. Near 0
- ☐ B. 25%
- ☐ C. 50%
- ☒ D. 75%
- ☐ E. 100%

Submit





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What is the probability that the unborn child will inherit one or more mutant alleles from the parents?

- ☐ A. Near 0 (0%)
- ☐ B. 25% (17%)
- ☒ C. 50% (7%)
- ☐ D. 75% (69%)
- ☐ E. 100% (4%)

Incorrect

Correct answer



69%

Answered correctly



02 mins, 50 secs

Time spent



10/04/2020

Last updated

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TUTOR

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Feedback



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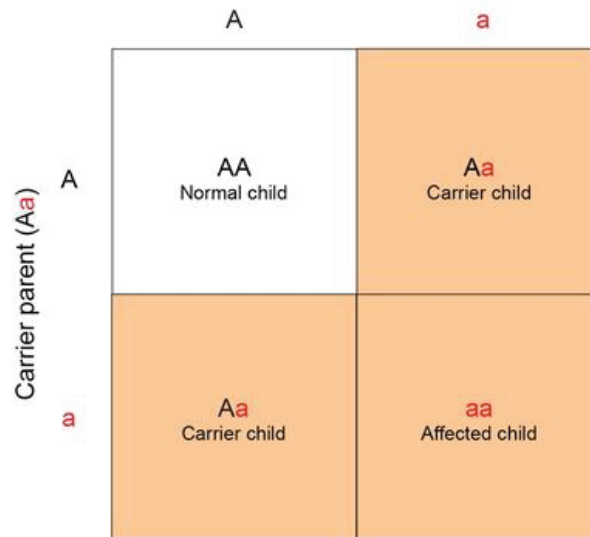


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Exhibit Display

Autosomal recessive inheritance

Carrier parent (Aa)



Offspring have 75% chance of inheriting at least 1 mutant allele

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The couple's 3-year-old son has **sickle cell anemia**, an **autosomal recessive** disorder that causes red blood cells to assume a sickle shape during times of hypoxic stress, resulting in painful and potentially life-threatening vasoocclusive crises. The disease can be diagnosed using **hemoglobin electrophoresis**, which is able to determine the different types of hemoglobin in a blood sample based on their electrical charge and the speed by which they move through the medium. The patient's electrophoresis results show a predominance of hemoglobin S (HbS), which is diagnostic for sickle cell disease.

In this case, both **parents are unaffected** and must be **heterozygous carriers** (Aa) of the disorder because they have an **affected child**. This means that each parent has a 50% chance of passing either a normal allele (A) or a mutant allele (a) to the offspring. The possible genotypes of the unborn child can be calculated using a Punnett square and are as follows:

- 25% chance of inheriting two normal alleles (AA, child is unaffected)
- 50% chance of inheriting one normal and one mutant allele (Aa or aA, child is a carrier)
- 25% chance of inheriting two mutant alleles (aa, child is affected)

Only the last 2 options result in the child inheriting a mutant allele, so the probability that the unborn child is carrying **one or more mutant alleles** is 75%.

(Choice B) The probability of the unborn child being affected is equivalent to the chance of inheriting two

The couple's 3-year-old son has sickle-cell anemia, an autosomal recessive disorder that causes red

Exhibit Display

Starting point of
electrophoresis



Sickle-cell anemia

Sickle-cell trait

Normal

Hb C

Hb S

Hb F

Hb A

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Only the last 2 options result in the child inheriting a mutant allele, so the probability that the unborn child is carrying **one or more mutant alleles** is 75%.

(Choice B) The probability of the unborn child being affected is equivalent to the chance of inheriting two mutant alleles from the carrier parents, which is 25%. However, this question asks for the probability that the unborn child will inherit one or more mutant alleles (ie, chance of having the disease or being a carrier).

Educational objective:

Sickle cell anemia is an autosomal recessive disease that results in recurrent episodes of anemia, jaundice, and painful swelling of the hands and feet. Offspring of carrier parents have a 25% chance of being affected and a 50% chance of being heterozygous carriers, resulting in a 75% chance of inheriting at least one mutant allele.

References

- [Hematologic Disorders: Sickle Cell Disease.](#)

Genetics

Subject

Genetics (General Principles)

System

Genetic inheritance

Topic

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A 28-year-old man is evaluated for abnormal movements of the hands and face. The patient reports that he started experiencing involuntary grimacing a year ago, which has gradually worsened. He is taking a selective serotonin reuptake inhibitor for major depression but has not taken any antipsychotic medications. His 52-year-old father was diagnosed with an inherited movement disorder 2 months ago. Physical examination shows normal strength and normal deep tendon reflexes. No sensory deficits are noted. Which of the following best explains the difference in disease presentation between this patient and his father?

- ☐ A. Anticipation
- ☐ B. Genomic imprinting
- ☐ C. Incomplete penetrance
- ☐ D. Microdeletion
- ☐ E. Mosaicism
- ☐ F. Pleiotropy





he started experiencing involuntary grimacing a year ago, which has gradually worsened. He is taking a selective serotonin reuptake inhibitor for major depression but has not taken any antipsychotic medications. His 52-year-old father was diagnosed with an inherited movement disorder 2 months ago. Physical examination shows normal strength and normal deep tendon reflexes. No sensory deficits are noted. Which of the following best explains the difference in disease presentation between this patient and his father?



- ☒ A. Anticipation (88%)
- ☐ B. Genomic imprinting (0%)
- ☐ C. Incomplete penetrance (5%)
- ☐ D. Microdeletion (0%)
- ☐ E. Mosaicism (1%)
- ☐ F. Pleiotropy (2%)

Correct



88%



29 secs



11/29/2020

Block Time Remaining: 00:13:16

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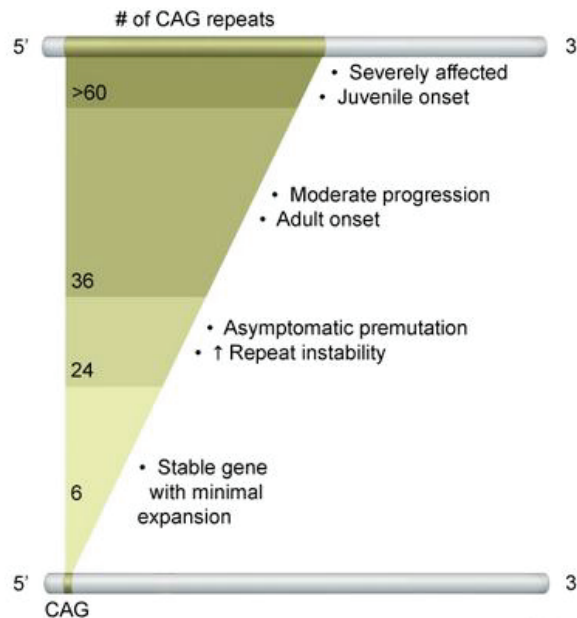
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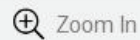


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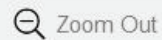
Anticipation in Huntington disease



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Zoom Out



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1





This patient presenting with involuntary movements, depression, and a family history of a movement disorder likely has **Huntington disease** (HD), which typically manifests with the triad of movement disorder (chorea), behavioral abnormalities (aggressiveness, apathy, or depression), and dementia. HD is caused by an expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats. Most patients develop symptoms in their 40s or 50s, but an earlier age of onset and more severe symptoms are associated with a larger number of **trinucleotide repeats**.

During spermatogenesis, CAG repeats in the abnormal *HTT* gene (chromosome 4p) can rapidly increase (much more than during oogenesis). Therefore, patients who receive an abnormal gene from their fathers tend to develop the disease earlier in life. The tendency for clinical symptoms to worsen and/or occur earlier in subsequent generations is called **anticipation**. Anticipation is common in disorders associated with trinucleotide repeats, as in Fragile X syndrome, myotonic dystrophy, and Friedreich ataxia.

(Choice B) Genomic imprinting is a selective inactivation of the genes of either maternal or paternal origin. It results in Prader-Willi and Angelman syndromes, which involve deletions of the same region on chromosome (15q) but have very different clinical manifestations due to the differential expression of parental genes. When the chromosome with the deleted region comes from the father, the lack of expression of maternally imprinted genes results in Prader-Willi syndrome. Likewise, deletions affecting





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Previous

Next

Full Screen

Tutorial

Lab Values

Notes

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expression of maternally imprinted genes results in Prader-willi syndrome. Likewise, deletions affecting the maternal chromosome result in Angelman syndrome due to absent expression of paternally imprinted genes.

(Choice C) HD is transmitted in an autosomal dominant pattern with complete penetrance, which means that a child who inherits the abnormal gene will inevitably develop Huntington disease.

(Choice D) Microdeletion is the loss of genetic material too small to be visible via light microscopy. For example, microdeletion of 22q11 is responsible for DiGeorge syndrome.

(Choice E) The presence of 2 populations of cells with different genotypes in one patient resulting in the mixed expression of disease is called mosaicism. Examples of mosaicism include milder forms of Turner (genotype 46XX/45X0), Klinefelter (46XY/47XXY), and Down syndromes.

(Choice F) Sometimes, one gene mutation leads to multiple, seemingly unrelated phenotypic abnormalities, a genetic phenomenon termed pleiotropy.

Educational objective:

An increased number of trinucleotide repeats on the *HTT* gene is associated with Huntington disease. The larger the number of repeats, the earlier the onset of the disease. Trinucleotide expansion occurs more frequently during paternal transmission, causing a genetic phenomenon called anticipation.



1



Feedback



Suspend



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A 12-year-old boy is evaluated in the clinic due to excessive bleeding following a tooth extraction. The patient also develops large bruises after only minor injury but has had no major bleeding episodes in the past. His maternal uncle died from an intracranial hemorrhage. Laboratory testing reveals decreased coagulation factor VIII activity levels. A referral is made to a clinical geneticist, who suspects that the patient has a deletion mutation in the enhancer sequence of the factor VIII gene. This mutation has resulted in decreased transcription of factor VIII by RNA polymerase II. Which of the following is the most accurate statement regarding the abnormal genetic sequence in this patient?

- ☐ A. It can be located upstream, downstream, or within introns of the gene
- ☐ B. It can function within only a short distance of the gene
- ☐ C. It directly binds RNA polymerase and general transcription factors
- ☒ D. It does not require protein binding to affect transcription
- ☐ E. It is required to initiate transcription

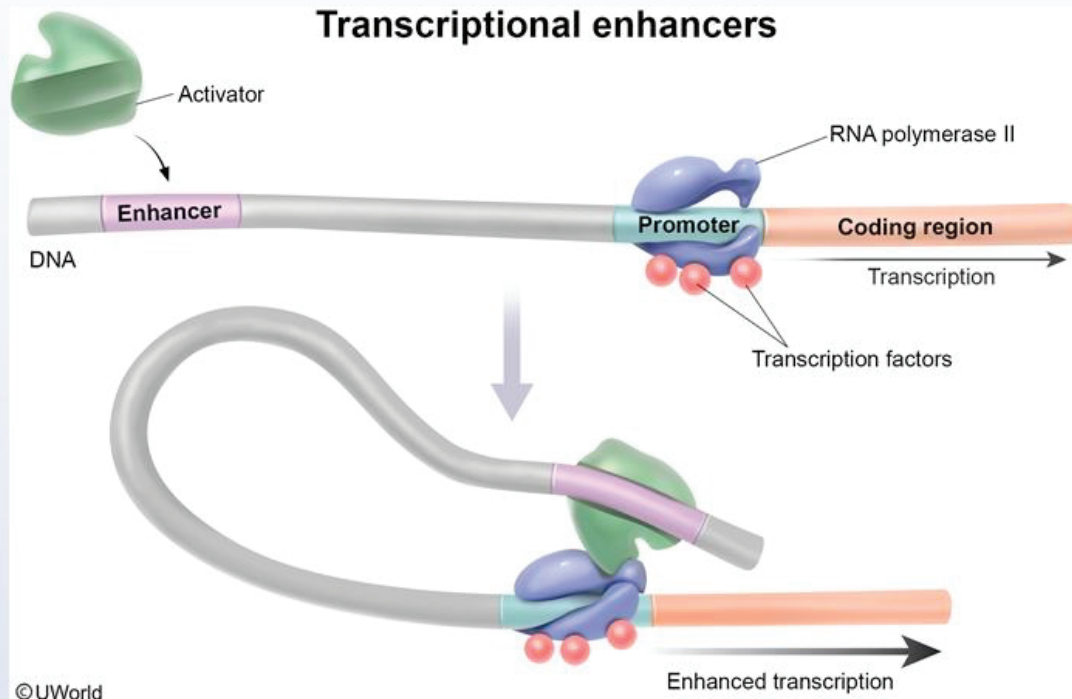
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A 12-year-old boy is evaluated in the clinic due to excessive bleeding following a tooth extraction. The patient also develops large bruises after only minor injury but has had no major bleeding episodes in the past. His maternal uncle died from an intracranial hemorrhage. Laboratory testing reveals decreased coagulation factor VIII activity levels. A referral is made to a clinical geneticist, who suspects that the patient has a deletion mutation in the enhancer sequence of the factor VIII gene. This mutation has resulted in decreased transcription of factor VIII by RNA polymerase II. Which of the following is the most accurate statement regarding the abnormal genetic sequence in this patient?

- ☒ A. It can be located upstream, downstream, or within introns of the gene (61%)
- ☐ B. It can function within only a short distance of the gene (7%)
- ☐ C. It directly binds RNA polymerase and general transcription factors (14%)
- ☐ D. It does not require protein binding to affect transcription (4%)
- ☐ E. It is required to initiate transcription (12%)





This patient has hemophilia A, an X-linked recessive disorder characterized by easy bruising and excessive bleeding due to a deficiency in coagulation factor VIII. The disorder can be caused by a variety of different



This patient has hemophilia A, an X-linked recessive disorder characterized by easy bruising and excessive bleeding due to a deficiency in coagulation factor VIII. The disorder can be caused by a variety of different mutations in the factor VIII gene, including deletions in the enhancer sequence.

In eukaryotic gene transcription, nuclear RNA polymerase II uses a DNA template to generate complementary mRNA, which is then processed and translated into protein. **Eukaryotic genes** have associated promoter and enhancer sequences that mediate transcription. Promoter sequences directly bind general transcription factors and RNA polymerase II upstream from the gene locus, which is necessary for the initiation of transcription (**Choices C and E**). There are 2 types of eukaryotic promoter regions: the TATA, or Hogness, box, which is located approximately 25 bases upstream from the gene being transcribed; and the CAAT box, which is 70-80 bases upstream from the gene.

In contrast to promoters, **enhancer sequences** bind activator proteins that facilitate bending of DNA. DNA bending allows activator proteins to interact with general transcription factors and RNA polymerase II at the promoter, increasing the **rate of transcription (Choice D)**. Enhancers can be located **upstream or downstream** from the gene being transcribed and may be near the gene or thousands of base pairs away (**Choice B**). They have also been identified both **within introns** of the gene being transcribed as well as on separate chromosomes. Silencers are similar to enhancers, but they decrease transcription rates by





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Lab Values



Notes



Calculator



Reverse Color



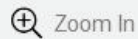
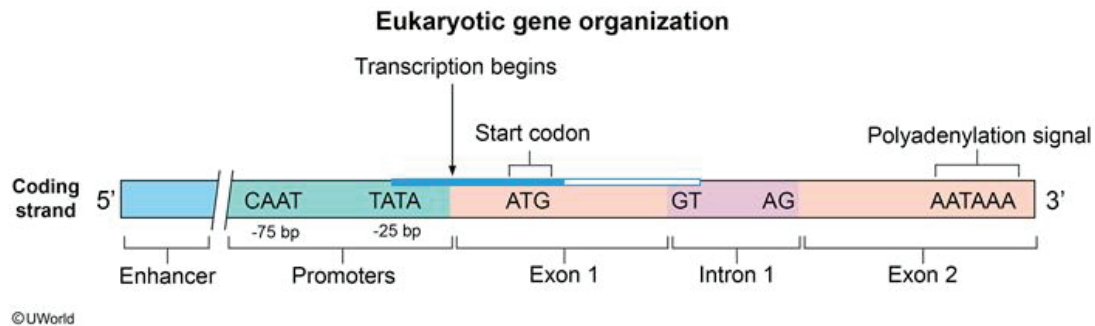
Text Zoom



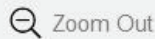
Settings

Enhanced transcription

Exhibit Display



Zoom In



Zoom Out



Reset



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Feedback



Suspend



End Block



Feedback



Suspend



End Block

bending allows activator proteins to interact with general transcription factors and RNA polymerase II at the promoter, increasing the **rate of transcription (Choice D)**. Enhancers can be located **upstream or downstream** from the gene being transcribed and may be near the gene or thousands of base pairs away **(Choice B)**. They have also been identified both **within introns** of the gene being transcribed as well as on separate chromosomes. Silencers are similar to enhancers, but they decrease transcription rates by binding repressor proteins.

Educational objective:

Enhancers and silencers may be located upstream, downstream, or within a transcribed gene; these gene sequences function to increase and decrease the rate of transcription, respectively. In contrast, promoter regions are typically located 25 or 75 bases upstream from their associated genes and function to initiate transcription.

References

- [Regulatory regions in DNA: promoters, enhancers, silencers, and insulators.](#)

Genetics

Genetics (General Principles)

Transcription

Subject

System

Topic



A 12-year-old Caucasian male with history of seizure disorder experiences several stroke-like episodes with residual neurological deficit. He also suffers from muscle weakness. Blood tests show increased serum lactate levels both post-exercise and at rest. This patient's condition is known to be maternally inherited. This patient's sister is also affected by the same disorder, but she displays very few symptoms. Which of the following is the most likely explanation for the variability in clinical presentation between the patient and his sister?

- ☐ A. Genetic imprinting
- ☐ B. Heteroplasmy
- ☐ C. Anticipation
- ☐ D. Low expression variability
- ☐ E. Female sparing

Submit



A 12-year-old Caucasian male with history of seizure disorder experiences several stroke-like episodes with residual neurological deficit. He also suffers from muscle weakness. Blood tests show increased serum lactate levels both post-exercise and at rest. This patient's condition is known to be maternally inherited. This patient's sister is also affected by the same disorder, but she displays very few symptoms. Which of the following is the most likely explanation for the variability in clinical presentation between the patient and his sister?

- ☐ A. Genetic imprinting (8%)
- ☒ B. Heteroplasmy (60%)
- ☐ C. Anticipation (2%)
- ☐ D. Low expression variability (15%)
- ☐ E. Female sparing (12%)

Correct



60%

Answered correctly



56 secs

Time Spent



01/30/2021

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Mitochondria have a small amount of their own DNA, called mitochondrial DNA (mtDNA), which can have deletions and point mutations just like regular DNA. Mitochondrial disorders (mutations in mtDNA) are unique in that they are exclusively inherited from one's mother. Recall that the ovum is relatively large and has many copies of mtDNA; whereas, the few copies of mtDNA present in sperm are lost during fertilization.

Mitochondrial diseases affect both male and female offspring with equal frequency (100%), but there are variable degrees of severity. This variability occurs because, during mitosis, mitochondria are randomly distributed between daughter cells. As a result, some cells contain mitochondria with mostly damaged mtDNA, while some contain mostly normal mitochondrial genomes. This mixture of two types of genetic material is called **heteroplasmy** and is responsible for the clinical variability of mitochondrial diseases.

The following mitochondrial syndromes are important:

1. *Leber hereditary optic neuropathy* leads to bilateral vision loss.
2. *Myoclonic epilepsy with ragged-red fibers*: myoclonic seizures and myopathy associated with exercise. Skeletal muscle biopsy shows irregularly shaped muscle fibers (ragged red fibers).
3. *Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)*. The clinical presentation of MELAS is described in this vignette.





3. *Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)*. The clinical presentation of MELAS is described in this vignette.

(Choice A) Genetic imprinting is a selective inactivation of paternal or maternal alleles. This phenomenon explains the differences in clinical presentation between Prader-Willi and Angelman syndromes.

(Choice C) Anticipation refers to the increase in severity of genetic disorders in subsequent generations. Anticipation is often seen in diseases involving an increased number of trinucleotide repeats, such as Huntington disease and Fragile X syndrome.

(Choice D) Variable expressivity refers to the differences in severity of autosomal dominant disorders. For example, a patient with Marfan syndrome may have only tall stature, while another patient with the same genetic defect will have tall stature, aortic root dilation, and lens dislocation. Variable expressivity is not a feature of mitochondrial diseases.

(Choice E) Female sparing is not characteristic of mitochondrial disorders. Both males and females are equally affected in mitochondrial disorders.

Educational Objective:

Mitochondrial diseases are characterized by exclusively-maternal inheritance. The variable severity of these diseases is explained by the random distribution of normal and mutated mitochondria between





(Choice C) Anticipation refers to the increase in severity of genetic disorders in subsequent generations.

Anticipation is often seen in diseases involving an increased number of trinucleotide repeats, such as Huntington disease and Fragile X syndrome.

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(Choice E) Female sparing is not characteristic of mitochondrial disorders. Both males and females are equally affected in mitochondrial disorders.

Educational Objective:

Mitochondrial diseases are characterized by exclusively-maternal inheritance. The variable severity of these diseases is explained by the random distribution of normal and mutated mitochondria between daughter cells during mitosis; as a result, some cells may have completely healthy mitochondria, while other cells contain mitochondria affected by genetic mutation (heteroplasmy). MELAS is a mitochondrial syndrome.





A 34-year-old woman with a history of recurrent urinary tract infections comes to the physician with dysuria and increased urinary frequency. Her urine culture grows colonies of Gram-negative bacteria. The bacteria are isolated and placed in a growth-enhancing nutrient solution, where they undergo rapid cellular division. As they are actively dividing, the bacterial cells are lysed and their DNA is extracted and purified. Analysis of the partially replicated DNA fragments shows the presence of uracil. This finding is most likely mediated by which of the following enzymes?

- ☐ A. DNA ligase
- ☐ B. DNA polymerase I
- ☐ C. DNA polymerase III
- ☐ D. Gyrase
- ☐ E. Helicase
- ☐ F. Primase

Submit

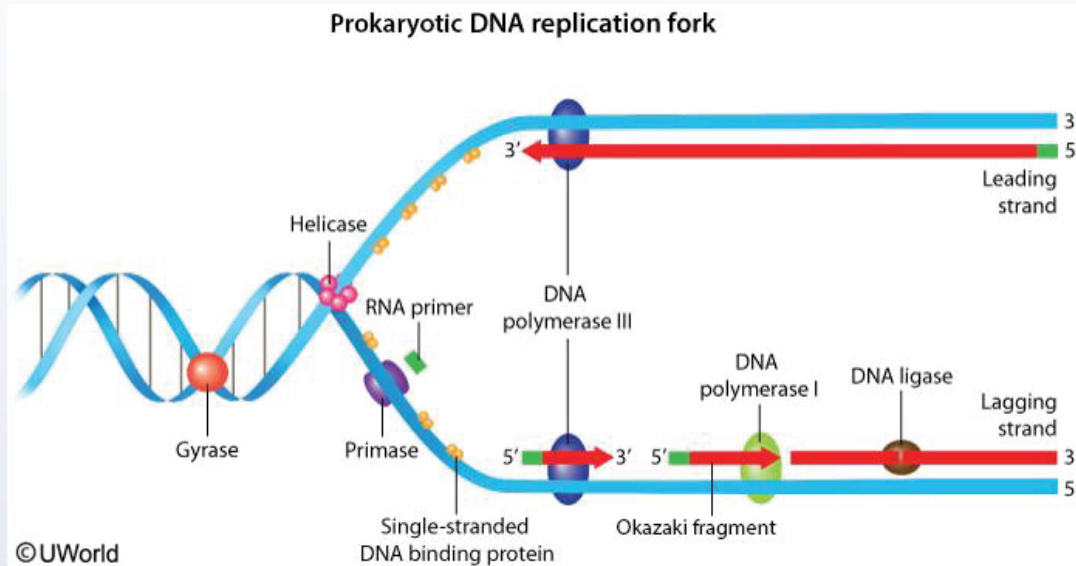




A 34-year-old woman with a history of recurrent urinary tract infections comes to the physician with dysuria and increased urinary frequency. Her urine culture grows colonies of Gram-negative bacteria. The bacteria are isolated and placed in a growth-enhancing nutrient solution, where they undergo rapid cellular division. As they are actively dividing, the bacterial cells are lysed and their DNA is extracted and purified. Analysis of the partially replicated DNA fragments shows the presence of uracil. This finding is most likely mediated by which of the following enzymes?

- ☐ A. DNA ligase (2%)
- ☐ B. DNA polymerase I (15%)
- ☐ C. DNA polymerase III (18%)
- ☐ D. Gyrase (2%)
- ☐ E. Helicase (1%)
- ☒ F. Primase (59%)





This question describes a scenario in which uracil is found in association with bacterial DNA during prokaryotic DNA replication. In general, uracil is found only in RNA, so the question essentially asks which enzyme involved in DNA synthesis catalyzes the formation of RNA strands. In prokaryotic DNA replication, primase (an RNA polymerase) is responsible for synthesizing a short RNA primer using the separated

prokaryotic DNA replication. In general, uracil is found only in RNA, so the question essentially asks which enzyme involved in DNA synthesis catalyzes the formation of RNA strands. In prokaryotic DNA replication, primase (an RNA polymerase) is responsible for synthesizing a short RNA primer using the separated strands of DNA at the replication fork as templates. DNA replication then proceeds, with DNA polymerase using the 3' hydroxyl group of the RNA primer as a starting point for synthesis. Primase is a crucial enzyme for bacterial replication as DNA polymerase cannot initiate DNA synthesis without this short nucleic acid sequence primer.

(Choice A) DNA ligase is the enzyme that repairs single-strand breaks in duplex DNA during DNA replication and repair.

(Choices B and C) During replication, DNA polymerase III is the primary enzyme responsible for synthesis of daughter DNA strands; DNA polymerase I functions chiefly to replace the RNA primers with DNA segments. Unlike DNA polymerase III, DNA polymerase I has 5'→3' exonuclease activity that can remove RNA primers and damaged DNA segments. The 3'→5' exonuclease activity of DNA polymerase I and III provides a proofreading function that fixes mismatched nucleotides in the newly formed daughter strands.

(Choices D and E) Helicase unwinds DNA at the replication fork. However, this process results in supercoiling of the DNA. DNA gyrase is a type II topoisomerase that helps to relieve the resultant strain.



(Choice A) DNA ligase is the enzyme that repairs single-strand breaks in duplex DNA during DNA replication and repair.

(Choices B and C) During replication, DNA polymerase III is the primary enzyme responsible for synthesis of daughter DNA strands; DNA polymerase I functions chiefly to replace the RNA primers with DNA segments. Unlike DNA polymerase III, DNA polymerase I has 5'→3' exonuclease activity that can remove RNA primers and damaged DNA segments. The 3'→5' exonuclease activity of DNA polymerase I and III provides a proofreading function that fixes mismatched nucleotides in the newly formed daughter strands.

(Choices D and E) Helicase unwinds DNA at the replication fork. However, this process results in supercoiling of the DNA. DNA gyrase is a type II topoisomerase that helps to relieve the resultant strain.

Educational objective:

Primase is a DNA-dependent RNA polymerase that incorporates short RNA primers into replicating DNA.

Biochemistry

Subject

Genetics (General Principles)

System

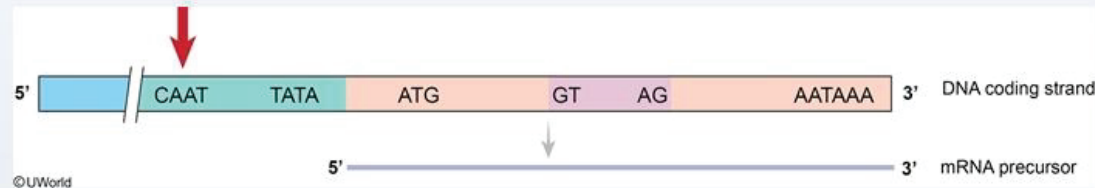
Transcription

Topic

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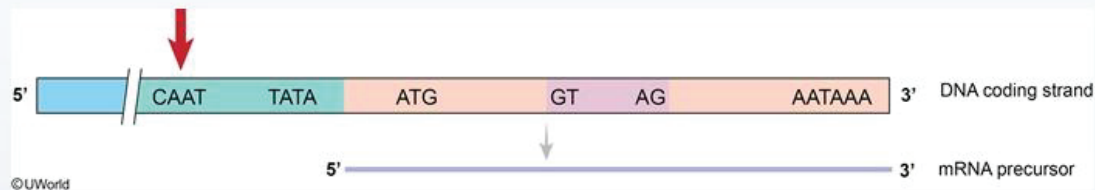
A 6-year-old girl with chronic anemia requiring repeated blood transfusions is undergoing genetic testing. The patient's mother and older sibling have a history of mild anemia. Her peripheral blood smear shows hypochromic, microcytic red blood cells, and hemoglobin electrophoresis reveals a predominance of hemoglobins F and A2. Sequencing of the β -globin gene is performed using the patient's erythroblast DNA. A schematic representation of the gene and its transcribed RNA is shown in the image below.



The base sequence indicated by the bold red arrow is responsible for which of the following functions?

- ☐ A. Enhancement of transcription
- ☐ B. Initiation of transcription
- ☐ C. Initiation of translation
- ☐ D. Repression of transcription

hemoglobins F and A2. Sequencing of the β -globin gene is performed using the patient's erythroblast DNA. A schematic representation of the gene and its transcribed RNA is shown in the image below.



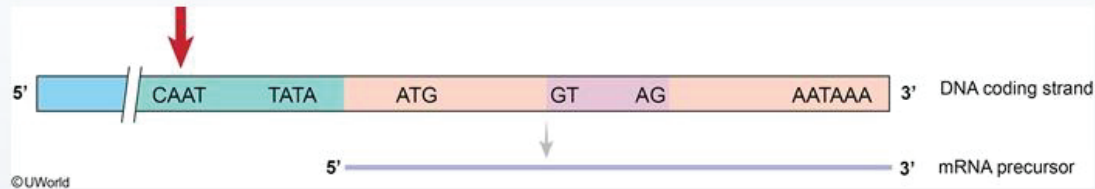
The base sequence indicated by the bold red arrow is responsible for which of the following functions?

- ☐ A. Enhancement of transcription
- ☐ B. Initiation of transcription
- ☐ C. Initiation of translation
- ☐ D. Repression of transcription
- ☐ E. Termination of transcription

Submit



hemoglobins F and A2. Sequencing of the β -globin gene is performed using the patient's erythroblast DNA. A schematic representation of the gene and its transcribed RNA is shown in the image below.



The base sequence indicated by the bold red arrow is responsible for which of the following functions?

- ☐ A. Enhancement of transcription (26%)
- ☒ B. Initiation of transcription (64%)
- ☐ C. Initiation of translation (4%)
- ☐ D. Repression of transcription (2%)
- ☐ E. Termination of transcription (2%)

Correct

64%
Answered correctly

50 secs
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02/17/2021
Last Updated

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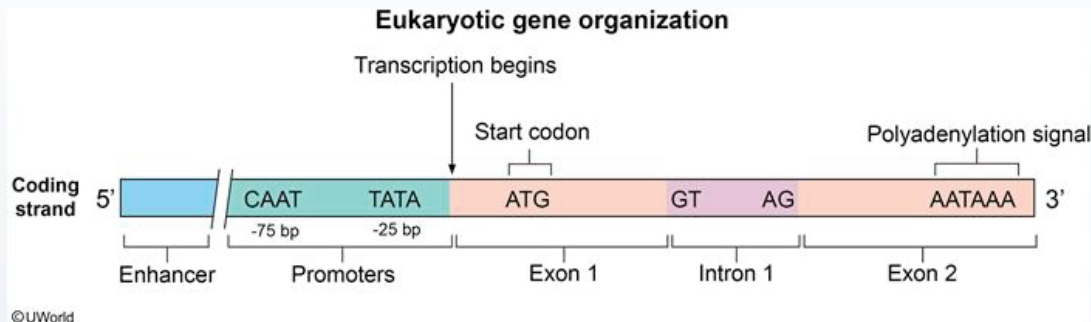
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This patient with chronic microcytic anemia requiring blood transfusions and a predominance of hemoglobins F and A2 on hemoglobin electrophoresis likely has beta-thalassemia, a hereditary blood disorder characterized by reduced β -globin chain production.

The base sequence indicated by the bold red arrow in this patient's β -globin gene represents the **CAAT box**, a highly conserved (consensus) sequence that functions as a **promoter of transcription** in the **eukaryotic** genome. It is typically located 70-80 bases upstream from the transcription start site. The Hogness (TATA) box is a second promoter region in the eukaryotic genome and is seen just to the right of the CAAT box in the above image. The TATA box is generally located 25 bases upstream from the transcription start site. Both the CAAT box and the TATA box promote initiation of transcription by acting as binding sites for general **transcription factors and RNA polymerase II**.





binding sites for general **transcription factors and RNA polymerase II**.

(Choice A) **Enhancer sequences** bind activator proteins that facilitate bending of DNA. DNA bending allows activator proteins to interact with general transcription factors and RNA polymerase II at the promoter, increasing the rate of transcription. Enhancers can be located upstream or downstream from the gene being transcribed and may be near the gene or thousands of base pairs away.

(Choice C) Translation is initiated in the cytoplasm when a ribosome recognizes the AUG (methionine) start codon on a mature mRNA strand. The Kozak consensus sequence plays a major role in initiation of the eukaryotic translation process.

(Choice D) Silencers are similar to enhancers, but they decrease transcription rates by binding repressor proteins.

(Choice E) Eukaryotic transcription termination is not completely understood. In prokaryotes, a palindromic code in the DNA template causes formation of a "hairpin" turn in the newly synthesized mRNA, which facilitates detachment of RNA polymerase from the DNA template.

Educational objective:

The TATA and CAAT boxes are promoters of transcription in eukaryotic cells and are located approximately 25 and 75 bases upstream from the transcription start site, respectively. They promote initiation of



gene being transcribed and may be near the gene or thousands of base pairs away.

(Choice C) Translation is initiated in the cytoplasm when a ribosome recognizes the AUG (methionine) start codon on a mature mRNA strand. The Kozak consensus sequence plays a major role in initiation of the eukaryotic translation process.

(Choice D) Silencers are similar to enhancers, but they decrease transcription rates by binding repressor proteins.

(Choice E) Eukaryotic transcription termination is not completely understood. In prokaryotes, a palindromic code in the DNA template causes formation of a "hairpin" turn in the newly synthesized mRNA, which facilitates detachment of RNA polymerase from the DNA template.

Educational objective:

The TATA and CAAT boxes are promoters of transcription in eukaryotic cells and are located approximately 25 and 75 bases upstream from the transcription start site, respectively. They promote initiation of transcription by serving as binding sites for transcription factors and RNA polymerase II.

References

- [RNA polymerase II transcription initiation: a structural view.](#)



A cell biologist is studying the role of ribonucleoproteins in normal cellular function. He prepares a cell extract using a specific cell type obtained from a 73-year-old man. Ribonucleoproteins are separated and purified from the cell extract for structural and functional analyses. These cells are found to express higher amounts of a particular protein in comparison to other cell types. This protein has reverse transcriptase activity that functions to add TTAGGG repeats to the 3' end of chromosomes. Which of the following cell types was most likely studied in this experiment?

- ☐ A. Epidermal basal cells
- ☐ B. Erythrocytes
- ☐ C. Myocardial cells
- ☐ D. Neurons
- ☐ E. Pancreatic β cells

Submit



A cell biologist is studying the role of ribonucleoproteins in normal cellular function. He prepares a cell extract using a specific cell type obtained from a 73-year-old man. Ribonucleoproteins are separated and purified from the cell extract for structural and functional analyses. These cells are found to express higher amounts of a particular protein in comparison to other cell types. This protein has reverse transcriptase activity that functions to add TTAGGG repeats to the 3' end of chromosomes. Which of the following cell types was most likely studied in this experiment?

- ☒ A. Epidermal basal cells (75%)
- ☐ B. Erythrocytes (3%)
- ☐ C. Myocardial cells (2%)
- ☐ D. Neurons (10%)
- ☐ E. Pancreatic β cells (7%)

Correct



75%

Answered correctly



56 secs

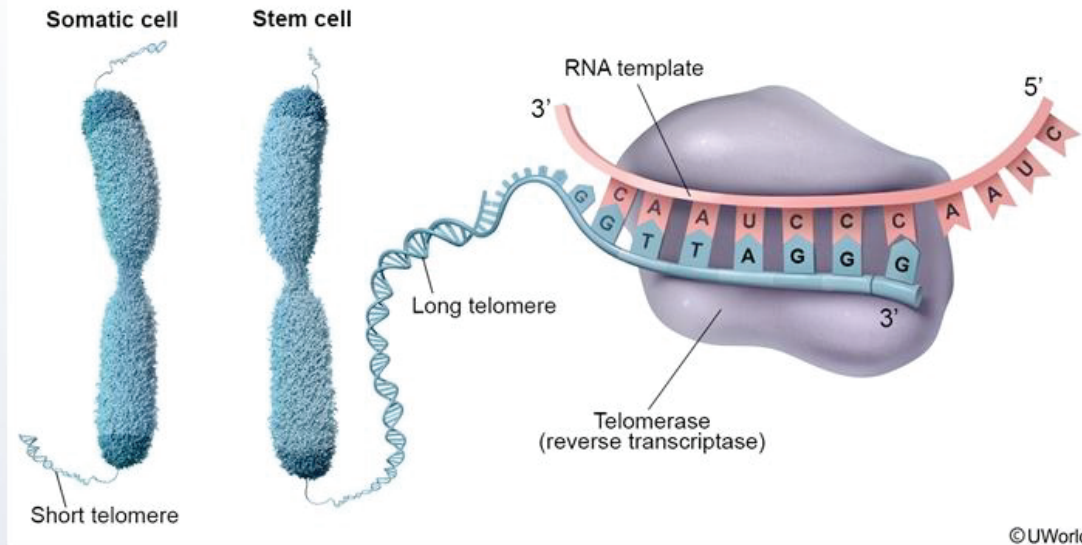
Time Spent



02/23/2021

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Telomerase is a ribonucleoprotein that adds **TTAGGG** repeats to the **3' end of chromosomes** (telomere region). It is similar to other reverse transcriptase enzymes in that it synthesizes single-stranded DNA using single-stranded RNA as a template (**RNA-dependent DNA polymerase**). Telomerase is composed of 2 main subunits, the telomerase reverse transcriptase (TERT) subunit and the telomerase RNA component (TERC). TERC is a "built-in" RNA template that is repeatedly read by the TERT subunit to add **TTAGGG** DNA repeats to the 3' end of chromosomes.



TTAGGG DNA sequence repeats to telomeres.

Stem cells have very **long telomeres** due to their high telomerase activity, allowing them to proliferate indefinitely in a controlled manner. In contrast, most terminally differentiated adult somatic cells (eg, myocardial cells, neurons, pancreatic β cells) have short telomeres as they do not express telomerase and their telomeres shorten with every cell division (**Choices C, D, and E**). Critical shortening in telomere length is thought to be a signal for programmed cell death. In fact, syndromes of premature aging (eg, Bloom syndrome) are associated with shortened telomeres. In contrast, cancer cells upregulate their telomerase activity, preventing cell death by maintaining their telomere length.

Stem cells are undifferentiated cells with the potential to differentiate into other cell types and can be classified as either embryonic or adult stem cells. Although embryonic stem cells are present in the very early stages of embryogenesis and can give rise to every cell type in adult humans (pluripotent), adult stem cells are present in most tissues and are generally responsible for replacing dead cells. For example, the epidermis is continuously replaced by stem cells present in the basal cell layers. Bone marrow stem cells similarly replace peripheral red and white blood cells.

(Choice B) Erythrocytes have no nuclei and therefore have no potential to divide.

Educational objective:



length is thought to be a signal for programmed cell death. In fact, syndromes of premature aging (eg,

Bloom syndrome) are associated with shortened telomeres. In contrast, cancer cells upregulate their telomerase activity, preventing cell death by maintaining their telomere length.

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(Choice B) Erythrocytes have no nuclei and therefore have no potential to divide.

Educational objective:

Critical shortening in telomere length can signal for programmed cell death. Telomerase is a reverse transcriptase (RNA-dependent DNA polymerase) that lengthens telomeres by adding TTAGGG repeats to the 3' end of chromosomes. Stem cells have long telomeres due to high telomerase activity, allowing them to proliferate indefinitely in a controlled manner.

References

• Telomere structure and telomerase in health and disease (review)



A 25-year-old nulligravid woman comes with her husband to the clinic for preconception genetic counseling. She has oculocutaneous albinism due to a homozygous *OCA2* gene mutation within the region of chromosome 15q12-q13. Examination shows pale hypopigmented skin with blonde hair. Eye examination shows faint brown irises. Her husband is 26 years old and has oculocutaneous albinism due to a biallelic *TYR* gene mutation at position 11q14.3. Examination of the husband shows complete absence of pigmentation in the skin, hair, and irises. The couple asks about their chance of having a child with oculocutaneous albinism and are told that the chance is 0%. Which of the following is the best explanation for this?

- ☐ A. Allelic heterogeneity
- ☐ B. Heteroplasmy
- ☐ C. Incomplete penetrance
- ☐ D. Linkage disequilibrium
- ☒ E. Locus heterogeneity
- ☐ F. Pleiotropy



counseling. She has oculocutaneous albinism due to a homozygous *OCA2* gene mutation within the region of chromosome 15q12-q13. Examination shows pale hypopigmented skin with blonde hair. Eye examination shows faint brown irises. Her husband is 26 years old and has oculocutaneous albinism due to a biallelic *TYR* gene mutation at position 11q14.3. Examination of the husband shows complete absence of pigmentation in the skin, hair, and irises. The couple asks about their chance of having a child with oculocutaneous albinism and are told that the chance is 0%. Which of the following is the best explanation for this?

- ☒ A. Allelic heterogeneity (0%)
- ☐ B. Heteroplasmy (0%)
- ☐ C. Incomplete penetrance (0%)
- ☐ D. Linkage disequilibrium (0%)
- ☒ E. Locus heterogeneity (100%)
- ☐ F. Pleiotropy (0%)

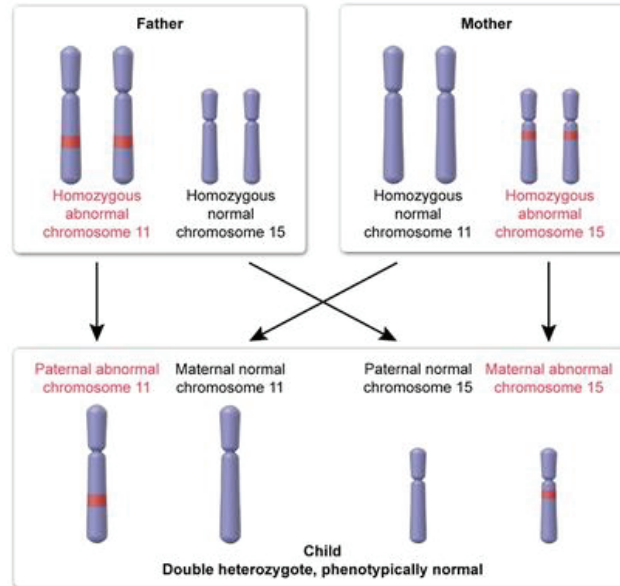
Incorrect

Locus heterogeneity in oculocutaneous albinism

Exhibit Display

Locus heterogeneity in oculocutaneous albinism

Mutations at different genetic loci result in similar phenotypes.



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This case is an example of **locus heterogeneity**, in which mutations at different genetic loci result in similar phenotypes. Both parents have oculocutaneous albinism, an inherited **autosomal recessive** disorder. However, although their phenotype is similar, their recessive mutations occur on **different chromosomes**.

In this case, the child would inherit one normal (paternal) allele and one abnormal (maternal) allele at location 15q12-q13 and one normal (maternal) allele and one abnormal (paternal) allele at location 11q14.3. Because the child would have **one normal, dominant allele at each location**, they would be a **double heterozygote** and therefore would not express an oculocutaneous albinism phenotype.

(Choice A) In contrast to this case, **allelic heterogeneity** describes *different mutations* at the *same genetic locus* causing similar phenotypes (eg, cystic fibrosis). Children born to parents who have autosomal recessive genetic conditions resulting from different mutations at the same genetic locus would inherit two abnormal copies of the gene and likely display the corresponding phenotype.

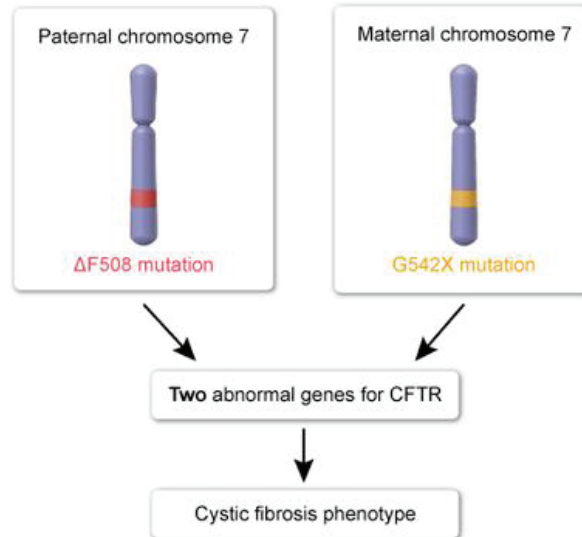
(Choice B) Mitochondrial diseases (eg, MELAS syndrome, Leber hereditary optic neuropathy) are maternally inherited. The variable severity of these diseases is explained by **heteroplasmy**, the random distribution of normal and mutated mitochondrial DNA between daughter cells during meiosis. As a result, some eggs may have completely healthy mitochondria while other cells contain mitochondria affected by



Exhibit Display

Allelic heterogeneity in cystic fibrosis

Different mutations at the same genetic locus result in the same phenotype.

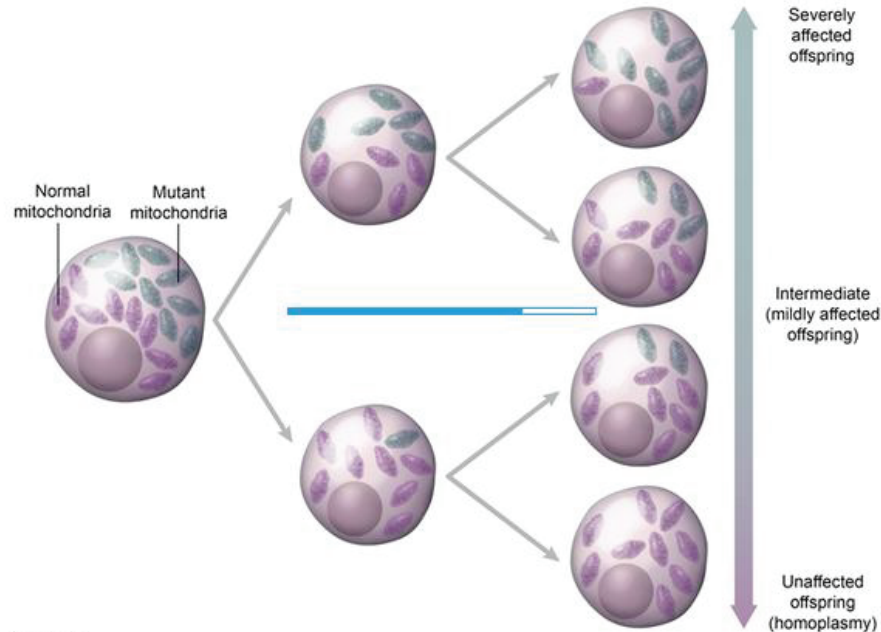


CFTR = cystic fibrosis transmembrane conductance regulator.

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Heteroplasmy





some eggs may have completely healthy mitochondria, while other cells contain mitochondria affected by genetic mutation.

(Choice C) Penetrance is the probability that a person with a given genotype will express its associated phenotype. Incomplete penetrance means that some individuals with an abnormal genotype will not express the corresponding phenotype (eg, breast cancer in individuals with *BRCA1/2* mutations).

(Choice D) Two allele loci are said to be in **linkage disequilibrium** when a pair of alleles is inherited together in the same gamete (haplotype) more often or less often than would be expected given random pairing. This most often occurs when the genes are in close physical proximity on the same chromosome.

(Choice F) The occurrence of multiple, seemingly unrelated phenotypic manifestations (often in different organ systems as a result of a single genetic defect) is termed pleiotrophy. Although this may apply to features of oculocutaneous albinism (eg, absence of melanin in skin, reduced visual acuity, nystagmus), it does not explain why a child of two affected parents would be unaffected.

Educational objective:

Locus heterogeneity describes when a similar phenotype is produced by mutations in different genetic loci (eg, oculocutaneous albinism).





A geneticist is performing an experiment to alter protein structures by incorporating modified amino acids into their polypeptide sequences. During the process, she incubates dermal fibroblasts in a medium containing fluorescently labeled lysine residues. After several hours, she finds that aminoacyl tRNA synthetase in the fibroblasts "loads" lysine residues onto tRNA molecules containing the anticodon UUU. This residue most likely attaches to tRNA at which of the following sites in the image shown below?

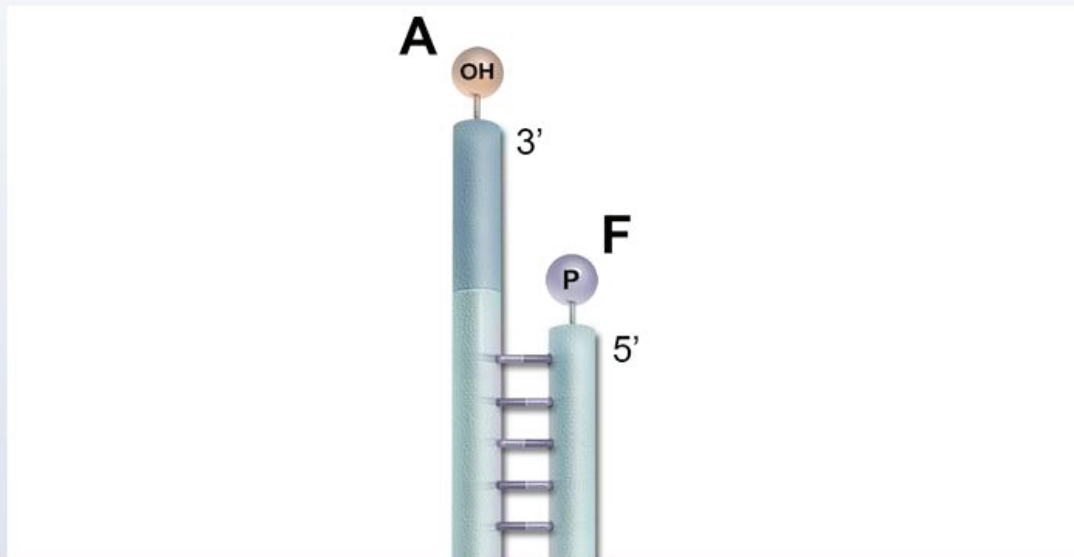
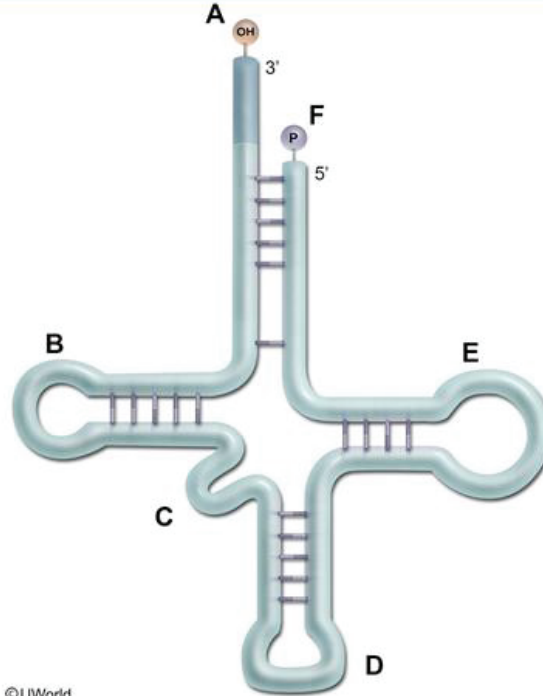


Exhibit Display



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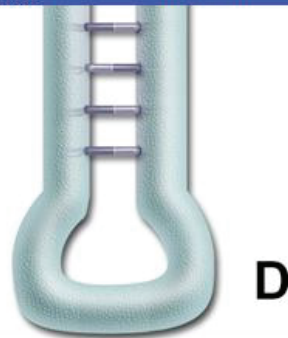
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- ☐ A.A
- ☐ B.B
- ☐ C.C
- ☐ D.D
- ☐ E.E
- ☐ F.F

Submit



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- ✓ ☒ A. A (67%)
- ☐ B. B (2%)
- ☐ C. C (2%)
- ☐ D. D (17%)
- ☐ E. E (2%)
- ☐ F. F (9%)

Correct

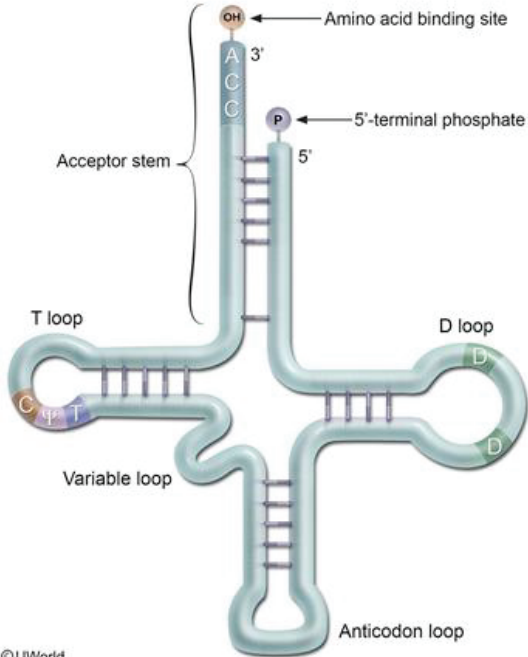
67%

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02/12/2021

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Secondary structure of tRNA



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The image above shows the "cloverleaf" secondary structure of **transfer RNA (tRNA)**, a small, noncoding subtype of RNA that is responsible for transporting amino acids to the site of protein synthesis and introducing them into the growing polypeptide chain at the correct locations.

The acceptor stem of tRNA is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. It contains the **CCA tail**, which is added to the 3' end of tRNA as a post-transcriptional modification and serves as the **amino acid binding site**. Aminoacyl tRNA synthetase is the enzyme responsible for "loading" the appropriate amino acid to the 3' terminal hydroxyl group of the CCA tail. The acceptor stem helps mediate correct tRNA recognition by the proper aminoacyl tRNA synthetase.

(Choice B) The T loop contains the T Ψ C sequence, which is necessary for the binding of tRNA to ribosomes. The T Ψ C sequence refers to the presence of the chemically modified bases ribothymidine and pseudouridine, and cytidine.

(Choice C) The variable loop contains a variable number of bases that lie between the T and anticodon loops. The variable loop is not present in all tRNAs.

(Choice D) The anticodon loop contains sequences that are complementary to the mRNA codon. During translation, the tRNA anticodon binds to the mRNA codon and assures placement of the proper amino acid





(Choice C) The variable loop contains a variable number of bases that lie between the T and anticodon loops. The variable loop is not present in all tRNAs.

(Choice D) The anticodon loop contains sequences that are complementary to the mRNA codon. During translation, the tRNA anticodon binds to the mRNA codon and assures placement of the proper amino acid in the growing polypeptide chain.

(Choice E) The D loop contains numerous dihydrouridine residues, which are modified bases often present in tRNA. The D loop (along with the acceptor stem and anticodon loop) facilitates correct tRNA recognition by the proper aminoacyl tRNA synthetase.

(Choice F) The 5' end of tRNA contains a terminal phosphate group that does not participate in amino acid or mRNA binding.

Educational objective:

The 3' CCA tail of tRNA serves as the amino acid binding site. Aminoacyl tRNA synthetase is the enzyme responsible for "loading" the appropriate amino acid to the 3' terminal hydroxyl group of the CCA tail.

References

- [CCA addition to tRNA: implications for tRNA quality control.](#)





A pharmaceutical researcher develops a new drug that affects bacterial protein synthesis. In an experiment, *Escherichia coli* is exposed to the drug and serially cultured in media containing tagged nucleotides and amino acids. It is found that the drug inhibits molecules that recognize the highlighted codon in the bacterial mRNA fragment shown in the image below.

5' --- ACG CUA CCA UUG CAA GUU AGC **UAA** AUA GCG UUC --- 3'

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Which of the following molecules is the most likely target of this drug?

- ☐ A. Charged tRNA
- ☐ B. Elongation factor 2
- ☐ C. Releasing factor 1
- ☐ D. snRNP
- ☐ E. Transcription factor II D
- ☐ F. Uncharged tRNA



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5' --- ACG CUA CCA UUG CAA GUU AGC UAA AUA GCG UUC --- 3'

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Which of the following molecules is the most likely target of this drug?

- ☐ A. Charged tRNA (15%)
- ☐ B. Elongation factor 2 (7%)
- ☒ C. Releasing factor 1 (56%)
- ☐ D. snRNP (5%)
- ☐ E. Transcription factor II D (3%)
- ☐ F. Uncharged tRNA (12%)



There are 64 codons in the genetic code, the majority of which code for amino acids. However, because there are only 20 amino acids, most have more than one codon. For example, GUU, GUC, GUA, and GUG all code for valine.

In addition, there are codons that call for initiation or **termination of protein synthesis**. The universal start codon is AUG, which codes for methionine. **UAA, UAG, and UGA** are **stop codons**, which do not code for amino acids or bind tRNA. Instead, when the ribosome encounters a stop codon, **releasing factor** proteins bind to the ribosome and stimulate release of the formed polypeptide chain and dissolution of the ribosome-mRNA complex.

(Choice A) Charged tRNA delivers amino acids to the protein synthesis complex. The anticodon on a tRNA molecule recognizes the corresponding codon on mRNA, assuring proper amino acid sequencing.

(Choice B) Elongation factors facilitate tRNA binding and the translocation steps of protein synthesis.

(Choice D) Transcription produces a pre-mRNA molecule containing both introns and exons. Splicing is a post-transcriptional modification in which introns are removed from pre-mRNA via small nuclear ribonucleoproteins (snRNPs).

(Choice E) Initiation of gene transcription is governed by the binding of transcription factors to the



(Choice B) Elongation factors facilitate tRNA binding and the translocation steps of protein synthesis.

(Choice D) Transcription produces a pre-mRNA molecule containing both introns and exons. Splicing is a post-transcriptional modification in which introns are removed from pre-mRNA via small nuclear ribonucleoproteins (snRNPs).

(Choice E) Initiation of gene transcription is governed by the binding of transcription factors to the regulatory region of the gene. Transcription factor II D binds to the TATA promoter sequence located ~25 bases upstream from the coding region of the gene.

(Choice F) During protein synthesis, uncharged tRNA (lacking an amino acid) does not interact with mRNA and ribosomes.

Educational objective:

Releasing factors recognize stop codons (eg, UAA, UAG, and UGA) and terminate protein synthesis. They facilitate release of the polypeptide chain from the ribosome and dissolution of the ribosome-mRNA complex.

References

- Terminating eukaryote translation: domain 1 of release factor eRF1 functions in stop codon recognition.
- Two-step model of stop codon recognition by eukaryotic release factor eRF1



A 5-year-old boy is being evaluated for progressive muscle weakness that has resulted in numerous recent falls. There is no family history of muscle disorders. Physical examination reveals bilateral calf enlargement. When the patient is asked to stand, he uses his hands and arms to help push himself to an upright position. Serum creatine kinase is 12,600 U/L (normal: 30-170 U/L). Molecular tests reveal a large muscle protein that is defective due to the loss of 508 amino acid residues. Genetic analysis reveals a single base substitution within exon 48 of the gene encoding this muscle protein. This patient's gene mutation has most likely resulted in which of the following mRNA codon changes?

- ☐ A. CUU → AUU
- ☐ B. UAA → UAG
- ☐ C. UAC → CAC
- ☐ D. UCA → UGA
- ☐ E. UUU → UUC

Submit





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- ☐ A. CUU → AUU (3%)
- ☐ B. UAA → UAG (19%)
- ☐ C. UAC → CAC (5%)
- ☒ D. UCA → UGA (69%)
- ☐ E. UUU → UUC (1%)





Mark



Previous



Next



Full Screen



Tutorial



Lab Values



Notes



Calculator



Reverse Color



Text Zoom



Settings

Types of DNA mutations

Silent	Base substitution codes for same amino acid
Missense	Base substitution codes for different amino acid
Conservative	Base substitution codes for different amino acid with similar chemical structure
Nonsense	Base substitution introduces premature stop codon
Nonstop	Base substitution within stop codon results in continued translation
Splice site	Mutation at splice site alters intron removal from pre-mRNA
Frameshift	Deletion/insertion of bases causes downstream misreading

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This young boy with progressive proximal muscle weakness, calf pseudohypertrophy, **Gowers sign**, and elevated creatine kinase likely has **Duchenne muscular dystrophy**, an X-linked recessive disorder.



1



Feedback



Suspend



End Block



This young boy with progressive proximal muscle weakness, calf pseudohypertrophy, **Gowers sign**, and elevated creatine kinase likely has **Duchenne muscular dystrophy**, an X-linked recessive disorder caused by mutations in the dystrophin gene. Although Duchenne muscular dystrophy is most commonly caused by **deletions** resulting in frameshift mutations, **nonsense mutations** may also occur, leading to the formation of a truncated dystrophin protein.

After messenger RNA (mRNA) is produced from DNA and posttranscriptionally modified, it is transported to the cytoplasm for translation into protein. mRNA is composed of groups of 3 sequential nucleotide bases known as codons. These nucleotide triplets code for specific amino acids and signal for the initiation (eg, start codon [AUG]) or termination of translation (eg, **stop codons [UAA, UAG, UGA]**). In this case, a single base substitution from UCA (serine) to UGA has introduced a **premature** stop codon in the middle of the protein sequence (nonsense mutation), resulting in early termination of protein synthesis.

Dystrophin normally links with actin fibers and provides mechanical reinforcement to glycoprotein complexes in the plasma membrane of skeletal muscle cells. Consequently, dystrophin dysfunction leads to increased breakdown of the sarcolemma, muscle fiber degeneration, and the clinical findings described above.





(Choices A and C) Changing CUU (leucine) to AUU (isoleucine) or UAC (tyrosine) to CAC (histidine) would result in an amino acid substitution at one position (missense mutation). The function of this protein may be altered depending on a variety of factors, but the ultimate size of the protein will remain the same. Missense mutations that result in the substitution of a new amino acid with similar chemical properties are called conservative mutations.

(Choice B) Changing UAA to UAG would not affect protein structure or function because both of these sequences are stop codons. Stop codons are normally located at the end of the translated region of mRNA.

(Choice E) Changing UUU to UUC would not affect the protein as both sequences code for phenylalanine. Point mutations that do not change the amino acid sequence of a protein are called silent mutations.

Educational objective:

Duchenne muscular dystrophy presents with progressive proximal muscle weakness in young boys due to increased muscle fiber degeneration. It is caused by frameshift mutations (most common) or nonsense mutations in the dystrophin gene that lead to the formation of a truncated, defective protein. Nonsense mutations introduce premature stop codons (eg. UAA, UAG, UGA) in the coding sequence of mRNA.





A 14-year-old boy experiences severe, prolonged bleeding following a tooth extraction. He also has a history of multiple episodes of painful joint swelling following minor trauma. His parents have no bleeding problems. Evaluation shows that the patient has an inherited disorder and that one of his parents is a genetic carrier. His older sister, who does not have this condition, is pregnant. She does not know the sex of her child. She asks about the risk that her child will be affected. Which of the following is the best estimate that this child will have the disease?

- ☐ A. Near 0
- ☐ B. 1/2
- ☐ C. 1/4
- ☐ D. 1/8
- ☐ E. 1/16
- ☐ F. 1/32

Submit



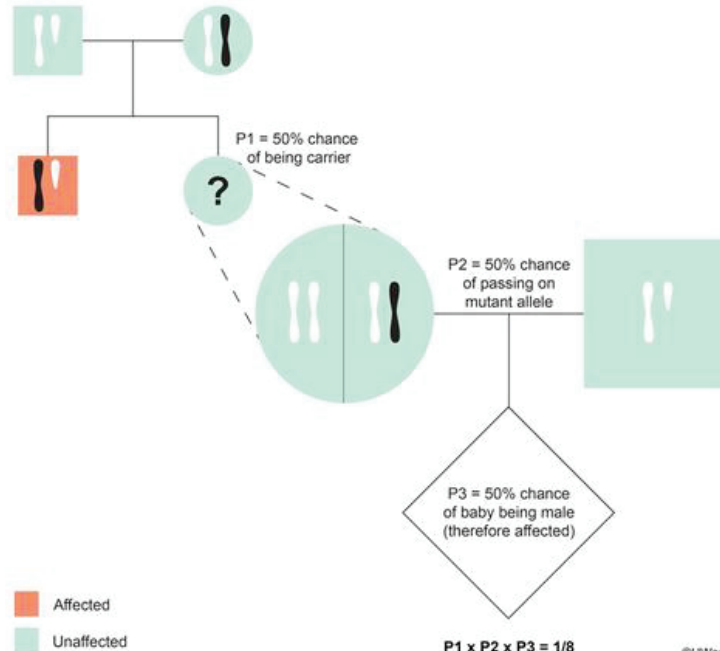
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- ☐ A. Near 0 (10%)
- ☐ B. 1/2 (8%)
- ☐ C. 1/4 (29%)
- ☒ D. 1/8 (45%)
- ☐ E. 1/16 (5%)
- ☐ F. 1/32 (1%)



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Hemophilia inheritance probability



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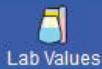
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This patient is a boy with excessive bleeding and hemarthroses, suggesting a diagnosis of **hemophilia A** or B. Both diseases are **X-linked recessive** coagulation factor deficiencies. The probability that his sister will give birth to an affected child can be calculated by multiplying the following probabilities:

- The probability (p1) that the sister is a **carrier** = 0.5. The patient's father does not carry the mutation on his X chromosome because he would be affected by the disease if he did. That means the mother carries the mutation on 1 of her 2 X chromosomes. This gives the daughter a 50% chance of having inherited the mutated X chromosome and therefore being a carrier.
- The probability (p2) that the offspring of a female carrier will **inherit** the X chromosome with the hemophilia gene = 0.5. Assuming the daughter is a carrier, the probability of passing on the mutant allele is 50% as only 1 of her 2 X chromosomes is passed to her offspring.
- The probability (p3) that his sister will have a **boy** = 0.5. If the sister's child is female, the child could be a carrier of the disease but would not be affected by it. If a male child inherits the mutated X chromosome, he will have the disease.

The probability that the sister will have an affected son is the probability that all 3 of the above events will take place (ie, the product of their individual probabilities): $p1 \times p2 \times p3 = 1/2 \times 1/2 \times 1/2 = 1/8$.

Educational Objective:





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

inherited the mutated X chromosome and therefore being a carrier.

- The probability (p_2) that the offspring of a female carrier will **inherit** the X chromosome with the hemophilia gene = 0.5. Assuming the daughter is a carrier, the probability of passing on the mutant allele is 50% as only 1 of her 2 X chromosomes is passed to her offspring.
- The probability (p_3) that his sister will have a **boy** = 0.5. If the sister's child is female, the child could be a carrier of the disease but would not be affected by it. If a male child inherits the mutated X chromosome, he will have the disease.

The probability that the sister will have an affected son is the probability that all 3 of the above events will take place (ie, the product of their individual probabilities): $p_1 \times p_2 \times p_3 = 1/2 \times 1/2 \times 1/2 = 1/8$.

Educational objective:

Given phenotypically normal parents, the probability that a female sibling of a male affected by an X-linked recessive disease will give birth to an affected child is $1/8$.

Genetics

Subject

Genetics (General Principles)

System

Genetic inheritance

Topic

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An 8-year-old boy of Ashkenazi Jewish ancestry is brought to the office after developing reduced sensitivity to pain, impaired tear formation, and orthostatic hypotension. Familial dysautonomia is suspected due to the patient's symptoms and heritage. This disorder is caused by loss of function of the IKAP protein, which is essential for development and survival of sensory and autonomic neurons. *IKAP* gene sequencing reveals a single nucleotide substitution that causes a guanine residue to be replaced by adenine at the highlighted position in the normal gene sequence shown below. Exon sequences are represented by capital letters and introns by lowercase letters.

```
5'-GTACAAACATTGCTGCTGGGAAAGCCGCCGCCACCATG
GGCTATGGGAGTGGTGGTAGCACTGGAGTTAACACCGAAATTG
GCAAGATCCGGGATGAAATGGTGG AACAGAACAGGAGAGAAC
ACCCCTTCAGCAAAACTAGATGAATTTAAAGTCATCTCCCTTA
TTTGCATTGCAGGCTGGATCATAAATATTGGGCACTTCAATGAC
CCGGTTGATGGAGGGTCCCTGGATCAGAGGTGCTATTTACTACT
TAA AATTGCAGTGGCCCTGGCTGTAGCAGGTGATTCCATTCTT
AAGgtctgcctgcagtcatcaccacctgcctggctctggaactcgcagaagaaaaatgcc
cattggaagcctcccgtctgtggaaacccttggtgtacttctgttatctgctcagacaagactgg
tacacttacaacaaaccagatgcagtctgcagGTACAAACATTGCTGCTGGGA
AAGCTATGGGAGTGGTGGTAGCAACTGGAGTTAAACCGAAATT
```





Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

highlighted position in the normal gene sequence shown below. Exon sequences are represented by capital letters and introns by lowercase letters.

```
5'-GTACAAACATTGCTGCTGGGAAAGCCGCCGCCGCCACCATG
GGCTATGGGAGTGGTGGTAGCACTGGAGTTAACACCGAAATTG
GCAAGATCCGGGATGAAATGGTGG AACAGAACAGGAGAGAAC
ACCCCTTCAGCAAAAAGTAGATGAATTTAAAGTCATCTCCCTTA
TTTGCATTGCAGGCTGGATCATAAATATTGGGCACTTCAATGAC
CCGGTTGATGGAGGGTCTTGGATCAGAGGTGCTATTTACTACT
TAAATTGCAGTGGCCCTGGCTGTAGCAGGTGATTCCATTCCCT
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GTCTGTGGAAACCCTTGGTTGACTTCTGTTATCTGCTCAGACAG
ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'
```



1



Feedback



Suspend



End Block



Mark

Previous

Next

Full Screen

Tutorial

Lab Values

Notes

Calculator

Reverse Color

Text Zoom

Settings

AAAGTCATCTCCCTTATTTGCATTGCAGTCTGGATCATAAATTTG
GGA CTTCAATGACCCGGTTCATGGAGGgtcmgatcagaggtgctatttacta
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ctgccGggctctGggaactgcgagaatggcaaagaaaaatgccattgttgaagcctcag
GTCTGTGGAAACCCTTGGTTGACTTCTGTTATCTGCTCAGACAG
ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'

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Which of the following is the most likely effect of this mutation?

- ☐ A. Decreased mRNA export to the cytosol
- ☐ B. Impaired ribosomal attachment to mRNA
- ☐ C. Incorrect splicing of pre-mRNA
- ☐ D. Increased degradation of mRNA by 5' exonucleases
- ☐ E. Translation of the 3'-untranslated region of mRNA

Submit

1



Feedback



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```
AAAGTCATCTCCCTTATTTGCATTGCAGTCTGGATCATAAATTTG
GGA CTTCAATGACCCGGTTCATGGAGGgtcmgatcagaggtgctatttacta
ctttaa aattgcagtgggccctggctgtagcagccattcctgaaggctgcctgcagtcacac
ctgccGggctctGggaactgcgagaatggcaaagaaaaatgccattgttcgaagcctcag
GTCTGTGGAAACCCTTGGTTGACTTCTGTTATCTGCTCAGACAG
ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'
```

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Which of the following is the most likely effect of this mutation?

- ☐ A. Decreased mRNA export to the cytosol (2%)
- ☐ B. Impaired ribosomal attachment to mRNA (4%)
- ☒ C. Incorrect splicing of pre-mRNA (86%)
- ☐ D. Increased degradation of mRNA by 5' exonucleases (3%)
- ☐ E. Translation of the 3'-untranslated region of mRNA (3%)

Correct

86%



17 secs

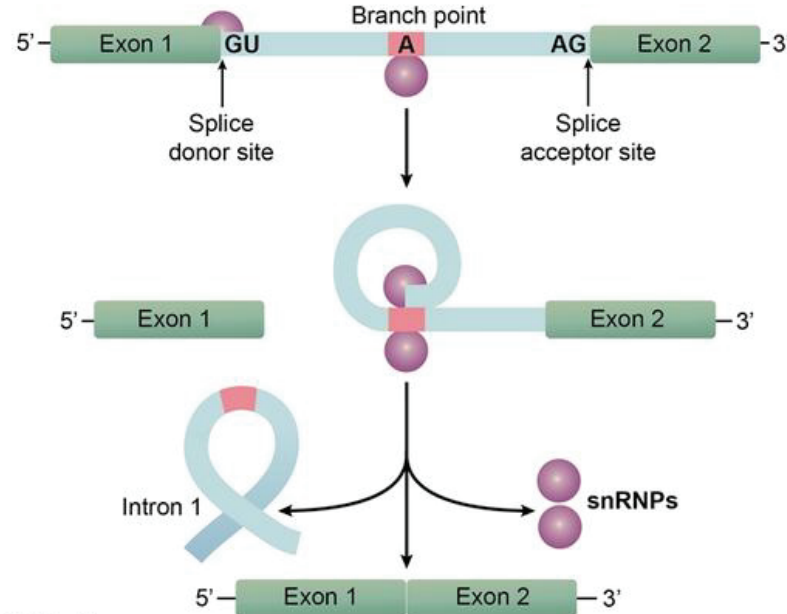


02/21/2021



Exhibit Display

Splicing of pre-mRNA



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Following transcription, pre-mRNA is the initial transcript that contains both intron and exon sequences. Before leaving the nucleus, pre-mRNA must be processed to mature mRNA by 3 post-transcriptional modifications: 5' methylguanosine capping, addition of a 3' polyadenine (Poly A) tail, and splicing.

Splicing is performed by **spliceosomes**, which are complexes of small nuclear ribonucleoproteins (snRNPs) and other proteins that assemble on pre-mRNA. Spliceosomes **remove introns** containing **GU** at the **5' splice site** and **AG** at the **3' splice site**. Initially, the 5' end of intron 1 (splice donor site) is cleaved and joined to the branch point. The freed 3'-OH of exon 1 then forms a phosphodiester bond with the 5'-phosphate at the splice acceptor site, joining exons 1 and 2. Mutations at splice sites may result in inappropriate removal of exons and retention of introns. This often leads to the formation of proteins with impaired structure and function as described in the case above.

(Choice A) Polyadenylation of the 3' end of mRNA is performed by the enzyme polyadenylate polymerase. This process stabilizes mRNA and helps it exit the nucleus.

(Choices B and D) In eukaryotes, translation is initiated when the small ribosomal subunit attaches to the 5' cap of mRNA and then scans for the AUG start codon within the Kozak consensus sequence. The 5' cap also protects against exonucleases and helps stabilize mRNA in the cytosol.



(Choice A) Polyadenylation of the 3' end of mRNA is performed by the enzyme polyadenylate polymerase. This process stabilizes mRNA and helps it exit the nucleus.

(Choices B and D) In eukaryotes, translation is initiated when the small ribosomal subunit attaches to the 5' cap of mRNA and then scans for the AUG start codon within the Kozak consensus sequence. The 5' cap also protects against exonucleases and helps stabilize mRNA in the cytosol.

(Choice E) Termination of polypeptide synthesis occurs at the 3 stop codons (UAA, UAG, UGA) in mRNA. Mutations in stop codons (nonstop mutations) can result in continued and inappropriate translation of mRNA into the 3'-untranslated region, producing an extremely long, nonfunctional polypeptide.

Educational objective:

Splicing is performed by spliceosomes, which remove introns containing GU at the 5' splice site and AG at the 3' splice site. Splice site mutations may result in inappropriate removal of exons and retention of introns, leading to the formation of dysfunctional proteins.

References

- Familial dysautonomia is caused by mutations of the IKAP gene.
- RNA splicing: disease and therapy.
- The pathobiology of splicing.



A 46-year-old woman is evaluated for a 2-month history of progressive abdominal distension, vague abdominal discomfort, and a bloating sensation. Physical examination shows moderate ascites. Laboratory evaluation reveals markedly elevated CA-125 and imaging studies show an ovarian mass. Molecular analysis of the malignant cells in ascitic fluid is performed, and these cells are found to have high telomerase activity. This enzyme promotes cell growth and malignancy by directly causing which of the following actions?

- ☐ A. Enhancing tissue invasion and metastasis
- ☐ B. Increasing transcription factor expression
- ☐ C. Preventing chromosomal shortening
- ☐ D. Promoting G1/S progression
- ☐ E. Sustaining angiogenesis

Submit



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- ☐ A. Enhancing tissue invasion and metastasis (1%)
- ☐ B. Increasing transcription factor expression (2%)
- ☒ C. Preventing chromosomal shortening (91%)
- ☐ D. Promoting G1/S progression (3%)
- ☐ E. Sustaining angiogenesis (0%)

Correct

 91%
Answered correctly 02 mins, 24 secs
Time Spent 03/01/2021
Last Updated

Block Time Remaining: 00:36:47

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Feedback



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End Block



Telomeres lie at the end of linear eukaryotic chromosomes and have tandem **repeat DNA sequences**, usually GT-rich repeats (eg, TTAGGG). They protect chromosomes from being recognized as damaged DNA, help to regulate gene expression, and participate in controlling cell replication and entry into senescence. As DNA polymerase cannot fully replicate the 3' end of the lagging chromosomal strands, cell division and aging lead to progressive DNA loss and telomere shortening at chromosomal ends. Once cells reach their maximum limit for proliferation (~50-70 divisions), the shortened telomeres trigger permanent growth arrest. Cell checkpoint genes (eg, *TP53*) become activated, and the critically short and dysfunctional telomeres lead to programmed cell death (apoptosis).

Telomerase is an RNA-dependent DNA polymerase that consists of 2 molecules, human telomerase reverse transcriptase (TERT) and telomerase RNA (TR or TERC). Telomerase synthesizes **telomeric DNA sequences** that can replace the lost **chromosomal ends** of the telomeres. As a result, the telomere can divide without reaching a limit. Normal human cells have absent telomerase activity except in cells that need to divide regularly (eg, germ cells, certain adult stem cells). However, >90% of cancer cells contain increased telomerase activity, allowing for continued proliferation without apoptosis.

(Choice A) Matrix metalloproteinases are proteases that degrade extracellular matrix proteins. They also modulate cell signaling by cleaving cell surface receptors, releasing apoptotic ligands, and inactivating chemokines/cytokines. These enzymes generally increase cell proliferation and allow for tissue invasion.





(Choice A) Matrix metalloproteinases are proteases that degrade extracellular matrix proteins. They also modulate cell signaling by cleaving cell surface receptors, releasing apoptotic ligands, and inactivating chemokines/cytokines. These enzymes generally increase cell proliferation and allow for tissue invasion and metastasis.

(Choice B) Proto-oncogenes often encode proteins involved in signal transduction in response to growth factors. Mutations in these genes can result in constitutive signal activation and increased transcription factor expression, stimulating cellular proliferation.

(Choice D) Cyclin D is a protein that is synthesized during the G1 phase of the cell cycle and helps promote the G1/S phase transition. Increased expression of cyclin D can result in unchecked cellular proliferation.

(Choice E) Vascular endothelial growth factor (VEGF) is a signal protein that helps create new blood vessels after injury. Cancer cells can overexpress VEGF to promote angiogenesis and allow for increased growth and metastasis.

Educational objective:

Telomerase is an RNA-dependent DNA polymerase that synthesizes telomeric DNA sequences that can replace the lost chromosomal ends of the telomeres. Cancer cells typically contain increased telomerase





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Educational objective:

Telomerase is an RNA-dependent DNA polymerase that synthesizes telomeric DNA sequences that can replace the lost chromosomal ends of the telomeres. Cancer cells typically contain increased telomerase activity to allow for continued proliferation.

References

- [Progress in structural studies of telomerase.](#)





Pharmacologic researchers develop a novel alkylating chemotherapeutic agent against glioblastoma multiforme. They find that malignant cells with methylation of the promotor region for the O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene are more susceptible to this drug than cells without methylation. Which of the following is the most likely function of the protein encoded by the gene?

- ☐ A. Induction of apoptosis
- ☐ B. Promotion of transcription
- ☐ C. Reducing major histocompatibility complex expression
- ☐ D. Repairing DNA damage
- ☐ E. Upregulation of telomerase

Submit





Pharmacologic researchers develop a novel alkylating chemotherapeutic agent against glioblastoma multiforme. They find that malignant cells with methylation of the promotor region for the O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene are more susceptible to this drug than cells without methylation. Which of the following is the most likely function of the protein encoded by the gene?

- ☐ A. Induction of apoptosis (0%)
- ☒ B. Promotion of transcription (0%)
- ☐ C. Reducing major histocompatibility complex expression (0%)
- ☒ D. Repairing DNA damage (100%)
- ☐ E. Upregulation of telomerase (0%)

IncorrectCorrect answer
D

Collecting Statistics

01 min, 41 secs
Time Spent03/12/2021
Last Updated

Explanation





Neoplasms develop genetic alterations that promote cellular growth and survival. Although this is partially mediated by inactivating genetic mutations in tumor suppressor genes (eg, p53), much of oncogenesis is mediated by the *altered expression* of unmutated genes, as follows:

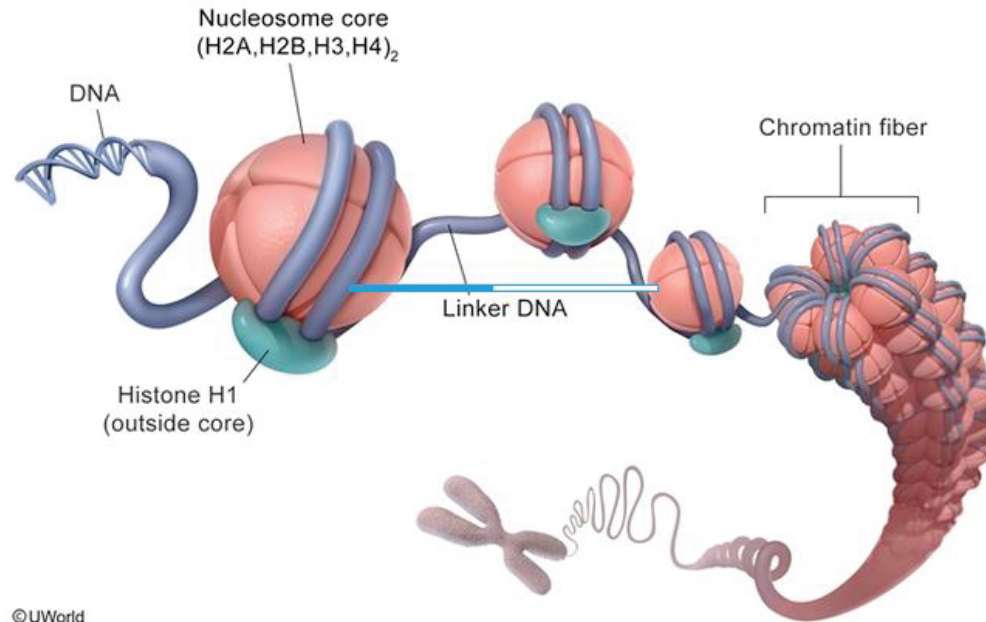
- **Histone modification:** Chromatin is organized into **nucleosomes**, which consist of a segment of DNA wrapped around 8 histone proteins. Modification of histones via acetylation, phosphorylation, or methylation can alter the availability of DNA for transcription, leading to increased or decreased gene expression. Histone modification allows tumors to increase prosurvival gene expression and reduce cell cycle arrest/apoptosis gene expression.
- **Transcription factor expression:** Transcription factors are activated by cell-surface ligand binding or by phosphorylation. Activated transcription factors travel to the nucleus and bind to the promoter/enhancer region of a specific gene, which alters RNA polymerase binding and subsequent gene expression. Tumors overexpress surface receptors (eg, HER2) that generate pro-survival transcription factors and underexpress surface receptors that generate cell cycle arrest/apoptotic signals.
- **CpG modifications:** Promoter regions typically contain a section of 200-2000 base pairs that primarily contain a cytosine followed a guanosine. **Methylation** of the CpG region **silences** the





Exhibit Display

Eukaryotic DNA organization



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- **CpG modifications:** Promoter regions typically contain a section of 200-2000 base pairs that primarily contain a cytosine followed a guanosine. **Methylation** of the CpG region **silences** the adjacent gene; neoplasms often methylate CpG promoter regions adjacent to genes that slow growth.

As part of oncogenesis, many **glioblastomas** methylate the CpG region adjacent to the O⁶-methylguanine-DNA methyltransferase (***MGMT***) gene, which generates a protein that **repairs damaged DNA** (eg, converts O⁶-methylguanine [a naturally occurring alkylation product] back to guanine). Although silencing ***MGMT*** creates a more permissive environment for DNA mutations to drive cancer growth, it also makes the cell more susceptible to **alkylating chemotherapy** (eg, temozolomide), since alkylating agents cause DNA damage that cannot be effectively repaired without ***MGMT***.

(Choice A) Mutation of tumor suppressing genes (eg, *BAX*) that trigger apoptosis or cell cycle arrest promotes oncogenesis. However, *MGMT* is not an apoptotic gene.

(Choice B) Prosurvival transcription factors are often overexpressed in cancer cells; however, *MGMT* methylation does not stimulate or inhibit transcription factor production.

(Choice C) As part of oncogenesis, tumors often reduce major histocompatibility complex class I expression, lowering the ability of cytotoxic T cells to recognize the abnormal proteins generated by





(Choice A) Mutation of tumor suppressing genes (eg, *BAX*) that trigger apoptosis or cell cycle arrest promotes oncogenesis. However, *MGMT* is not an apoptotic gene.

(Choice B) Prosurvival transcription factors are often overexpressed in cancer cells; however, *MGMT* methylation does not stimulate or inhibit transcription factor production.

(Choice C) As part of oncogenesis, tumors often reduce major histocompatibility complex class I expression, lowering the ability of cytotoxic T cells to recognize the abnormal proteins generated by cancerous cells. This process is not mediated by *MGMT*.

(Choice E) Increased telomerase activity helps promote cancer cell longevity; telomerase activity is frequently increased in tumors, but it is not mediated by *MGMT*.

Educational objective:

Cancer cells alter expression of genes controlling survival and replication by histone modification, transcription factor expression, and CpG methylation. Methylation of the CpG region adjacent to the *MGMT* gene, which produces an enzyme that repairs DNA, makes tumor cells much more susceptible to alkylating chemotherapy.

References

- [MGMT gene silencing and benefit from temozolomide in glioblastoma](#)

